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(57) Abstract

The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against interleukin-1 and apoptosis-mediated diseases, including inflammatory diseases, autoimmune diseases, proliferative, infectious, and degenerative diseases. This invention also relates to methods for inhibiting ICE activity and methods for treating interleukin-1 mediated diseases using the compounds and compositions of this invention.

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INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME

TECHNICAL FIELD OF THE INVENTION

The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme ("ICE"). This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against interleukin-1- ("IL-1") and apoptosis-mediated diseases, including inflammatory diseases, autoimmune diseases, proliferative disorders, infectious diseases, and degenerative diseases. This invention also relates to methods for inhibiting ICE activity and methods for treating interleukin-1- and apoptosis-mediated diseases using the compounds and compositions of this invention.

BACKGROUND OF THE INVENTION

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and

chondrocytes, basophil and eosinophil degranulation and neutrophil activation. Oppenheim, J.H. et al, Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. For example, in rheumatoid arthritis, IL-1 is both a mediator of inflammatory symptoms and of the destruction of the cartilage proteoglycan in afflicted joints. IL-1 is also a highly potent bone resorption agent. It is alternativly referred to as "osteoclast activating factor" in destructive bone diseases such as osteoarthritis and multiple myeloma. Bataille, R. et al., Int. J. Clin. Lab. Res., 21, p. 283 (1992). In certain proliferative disorders, such as acute myelogenous leukemia and multiple myeloma, IL-1 can promote tumor cell growth and adhesion. In these disorders, IL-1 also stimulates production of other cytokines such as IL-6, which can modulate tumor development. Tartour et al., Cancer Res. 54, 6243 (1994).

IL-1 is predominantly produced by peripheral blood monocytes as part of the inflammatory response and exists in two distinct agonist forms, IL-1α and IL-1β. Mosely, B.S. et al., Proc. Nat. Acad. Sci., 84, pp. 4572-4576 (1987); Lonnemann, G. et al., Eur.J. Immunol., 19, pp. 1531-1536 (1989).

IL-1β is synthesized as a biologically inactive precursor, pIL-1β. pIL-1β lacks a conventional leader sequence and is not processed by a signal peptidase. March, C.J., Nature, 315, pp. 641-647 (1985). Instead, pIL-1β is cleaved by interleukin-1β converting enzyme ("ICE") between Asp-

116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., J. Biol. Chem., 265, pp. 14526-14528 (1992); A.D. Howard et al., J. Immunol., 147, pp. 2964-2969 (1991).

ICE is a cysteine protease localized primarily in monocytes. It converts precursor IL-1β to the mature form. Black, R.A. et al., FEBS Lett., 247, pp. 386-390 (1989); Kostura, M.J. et al., Proc. Natl. Acad. Sci. USA, 86, pp. 5227-5231 (1989). Processing by ICE is also necessary for the transport of mature IL-1β through the cell membrane. ICE, or its homologues, also appears to be involved in the regulation of cell death or apoptosis. Yuan, J. et al., Cell, 75, pp. 641-652 (1993); Miura, M. et al., Cell, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., J. Cell Biochem., 17B, p. 117 (1993). In particular, ICE or ICE homologues are thought to be associated with the regulation of apoptosis in neurogenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259, pp. 760-762 (1993); Gagliardini, V. et al., Science, 263, pp. 826-828 (1994).

ICE has been demonstrated to mediate apoptosis (programmed cell death) in certain tissue types. Steller, H., Science, 267, p. 1445 (1995); Whyte, M. and Evan, G., Nature, 376, p. 17 (1995); Martin, S.J. and Green, D.R., Cell, 82, p. 349 (1995); Alnemri, E.S., et al., J. Biol. Chem., 270, p. 4312 (1995); Yuan, J. Curr. Opin. Cell Biol., 7, p. 211 (1995). Therapeutic applications for inhibition of apoptosis may include treatment of Alzheimer's disease, Parkinson's disease, stroke, mycardial infarction,

spinal atrophy, and aging. A transgenic mouse with a disruption of the ICE gene is deficient in Fas-mediated apoptosis. Kuida, et al. (1995). This activity of ICE is distinct from its role as the processing enzyme for pro-IL-1β. It is conceivable that in certain tissue types, inhibition of ICE may not affect secretion of mature IL-1β, but may inhibit apoptosis.

ICE has been previously described as a heterodimer composed of two subunits, p20 and p10 (20kDa and 10kDa molecular weight, respectively). These subunits are derived from a 45kDa proenzyme (p45) by way of a p30 form, through an activation mechanism that is autocatalytic. Thornberry, N.A. et al., Nature, 356, pp. 768-774 (1992). The ICE proenzyme has been divided into several functional domains: a prodomain (p14), a p22/20 subunit, a polypeptide linker and a p10 subunit. Thornberry et al., supra; Casano et al., Genomics, 20, pp. 474-481 (1994).

Full length p45 has been characterized by its cDNA and amino acid sequences. PCT patent applications WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and amino acid sequences are also known. Thornberry et al., supra. Murine and rat ICE have also been sequenced and cloned. They have high amino acid and nucleic acid sequence homology to human ICE. Miller, D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci., 90, pp. 1809-1813 (1993). The three-dimensional structure of ICE has been determined at atomic resolution by X-ray crystallography. Wilson, K.P., et al., Nature, 370, pp. 270-275 (1995). The active enzyme exists as a tetramer of two p20 and two p10 subunits.

Additionally, there exist human homologs of ICE with sequence similarities in the active site regions of the enzymes. Such homologs include TX (or ICE_{rel-II} or ICH-2) (Faucheu, et al., EMBO J., 14, p. 1914 (1995); Kamens J., et al., J. Biol. Chem., 270, p. 15250; Nicholson et al., J. Biol. Chem., 270 15870 (1995)), TY (or $ICE_{rel-III}$) (Nicholson et al., J. Biol. Chem., 270, p. 15870 (1995)), ICH-1 (or Nedd-2) (Wang, L. et al., Cell, 78, p. 739 (1994)), MCH-2, (Fernandes-Alnemri, T. et al., Cancer Res., 55, p. 2737 (1995), CPP32 (or YAMA or apopain) (Fernandes-Alnemri, T. et al., J. Biol. Chem., 269, p. 30761 (1994); Nicholson, D.W. et al., Nature, 376, p. 37 (1995)), and CMH-1 (or MCH-3) (Lippke, et al., J. Biol Chem., (1996); Fernandes-Alnemri, T. et al., Cancer Res., (1995)). Each of these ICE homologs, as well as ICE itself, is capable of inducing apoptosis when overexpressed in transfected cell lines. Inhibition of one or more of these homologs with the peptidyl ICE inhibitor Tyr-Val-Ala-Asp-chloromethylketone results in inhibition of apoptosis in primary cells or cell lines. Lazebnik et al., Nature, 371, p. 346 (1994). The compounds described herein are also capable of inhibiting one or more homologs of ICE (see example). Therefore, one can envisage using these compounds to inhibit apoptosis in tissue types that contain ICE homologs, but which do not contain active ICE or produce mature IL-1 β.

ICE inhibitors represent a class of compounds useful for the control of inflammation or apoptosis or both. Peptide and peptidyl inhibitors of ICE have been described. PCT patent applications WO 91/15577; WO 93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and European patent application 0 547 699. Such peptidyl

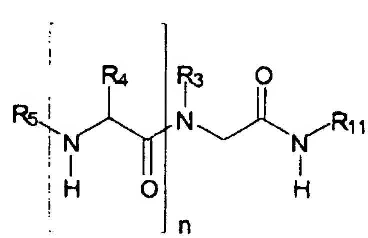
inhibitors of ICE have been observed to block the production of mature IL-1β in a mouse model of inflammation (Ku, et al. or vide infra) and to suppress growth of leukemia cells *in vitro* (Estrov, et al., Blood, 84, p. 380a (1994)).

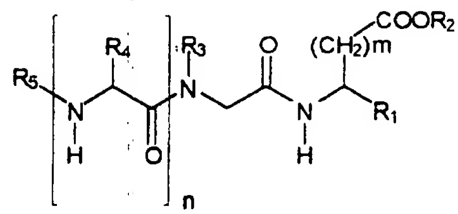
Accordingly, the need exists for compounds that can effectively inhibit the action of ICE *in vivo*, for use as agents for preventing and treating chronic and acute forms of IL-1-mediated diseases, apoptosis-mediated diseases, as well as inflammatory, autoimmune, bone-destructive, proliferative, infectious, degenerative, or necrotic diseases.

SUMMARY OF THE INVENTION

The present invention provides novel classes of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of ICE. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as antibiotics, immunomodulators or other anti-inflammatory agents, for the treatment or prophylaxis of diseases mediated by IL-1 or by apoptosis. According to a preferred embodiment, the compounds of this invention are capable of binding to the active site of ICE and inhibiting the activity of that enzyme.

It is a principal object of this invention to provide novel classes of inhibitors of ICE represented by formulas:

α  , and

β  ,

wherein the various substituents are described herein.

ABBREVIATIONS AND DEFINITIONS

Abbreviations

Designation	Reagent or Fragment
Ala	alanine
Arg	arginine
Asn	asparagine
Asp	aspartic acid
Cys	cysteine
Gln	glutamine
Glu	glutamic acid
Gly	glycine
His	histidine
Ile	isoleucine
Leu	leucine
Lys	lysine
Met	methionine
Phe	phenylalanine
Pro	proline
Ser	serine
Thr	threonine
Trp	tryptophan
Tyr	tyrosine

Val	valine
Ac_2O	acetic anhydride
n-Bu	normal-butyl
DMF	dimethylformamide
DIEA	*N,N*-diisopropylethylamine
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_2O	diethyl ether
EtOAc	ethyl acetate
Fmoc	9-fluorenylmethyoxycarbonyl
HBTU	O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBT	1-hydroxybenzotriazole hydrate
MeOH	methanol
TFA	trifluoroacetic acid

Definitions

The following terms are employed herein:

The term "active site" refers to any or all of the following sites in ICE: the substrate binding site, the site where an inhibitor binds and the site where the cleavage of substrate occurs.

The term "alkenyl", alone or in combination, refers to a straight-chain or branched-chain alkenyl radical containing from 2 to 10, carbon atoms. Examples of such radicals include, but are not limited to, ethenyl, E- and Z-propenyl, isopropenyl, E- and Z-butenyl, E- and Z- isobutenyl, E- and Z-pentenyl, decenyl and the like.

The term "alkynyl", alone or in combination, refers to a straight-chain or branched-chain alkynyl

radical containing from 2 to 10, carbon atoms. Examples of such radicals include, but are not limited to, ethynyl (acetylenyl), propynyl, propargyl, butynyl, hexynyl, decynyl and the like.

The term "substitute" refers to the replacement of a hydrogen atom in a compound with a substituent group.

The term "K_i" refers to a numerical measure of the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values of K_i reflect higher effectiveness. The K_i value is a derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The term "patient" as used in this application refers to any mammal, especially humans.

The term "pharmaceutically effective amount" refers to an amount effective in treating or ameliorating an IL-1- or apoptosis-mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening IL-1- or apoptosis-mediated disease in a patient.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon administration to a recipient, is capable of providing

(directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

Pharmaceutically acceptable salts of the compounds of this invention include, for example, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and $N-(C_{1-4}\ alkyl)_4^+$ salts.

This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such

quaternization.

The ICE inhibitors of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be depicted in a particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

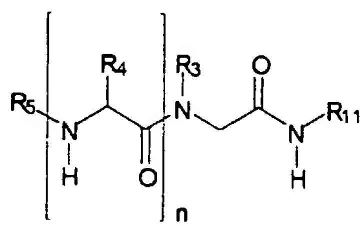
The ICE inhibitors of this invention may comprise structures which may optionally be substituted at carbon, nitrogen or other atoms by various substituents. Such structures may be singly or multiply substituted. Preferably, the structures contain between 0 and 3 substituents. When multiply substituted, each substituent may be picked independently of any other substituent as long as the combination of substituents results in the formation of a stable compound.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth.

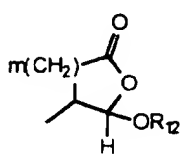
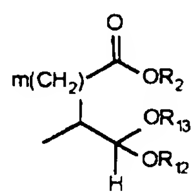
The ICE inhibitors of one embodiment (A) of this invention are those of formula (α):

α 

wherein:

$n = 0, 1,$ or 2;

R_{11} is:

(a)  , or (b)  ;

m is 1 or 2;

R_{12} and R_{13} are independently selected from the group consisting of $-R_7$, $-C(O)-R_7$, and $-C(O)-N(H)-R_7$, or R_{12} and R_{13} taken together form a 4-8-membered saturated cyclic group;

R_2 is -H or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar, -OH, $-OR_7$, -C(O)-OH, $C(O)-NH_2$, or $-OR_5$;

R_7 is selected from the group consisting of -Ar, a $-C_{1-6}$ straight or branched alkyl group optionally substituted with -Ar, a $-C_{1-6}$ straight or branched alkenyl group optionally substituted with Ar, and a $-C_{2-6}$ straight or branched alkynyl group optionally substituted with Ar;

R_5 is selected from the group consisting of:
$-C(O)-R_7$,
$-C(O)-OR_9$,
$-C(O)-N(R_9)(R_{10})$,
$-S(O)_2-R_7$,
$-C(O)C(O)-R_7$,
$-R_7$, and
-H;

each Ar is a cyclic group independently selected from the set consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl and a heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyraxolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-

naphthyridinyl, peridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl, and the aromatic group is optionally singly or multiply substituted with -F, -Cl, -Br, -I, $-OR_{14}$, $-NO_2$, $-S(O_2)-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

each R_{14} is -H or a C_{1-6} straight or branched alkyl group;

each R_9 and R_{10} is independently selected from the group consisting of -H, -Ar, and a C_{1-5} straight or branched alkyl group optionally substituted with -Ar;

each R_4 is a $-C_{1-5}$ straight or branched alkyl group optionally substituted with -Ar or -W;

W is $-OR_9$, $-SR_9$, $-N(H)C(NR_9)N(R_9)(R_{10})$, $-C(O)-OR_9$, or $-N(R_9)(R_{10})$;

R_3 is $-CH_2Ar$ or a 5 to 15-membered non-aromatic cyclic group which contains between 1 and 3 rings, and which optionally contains between 0 and 2 endocyclic oxygen atoms, sulfur atoms, or nitrogen atoms, and wherein the cyclic group is optionally fused with Ar;

provided that when -Ar is substituted with a group containing R_9 or R_{10} which comprises one or more addditional -Ar groups, the -Ar groups are not substituted with a group containing R_9 or R_{10};

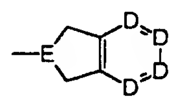
Preferred compounds of this embodiment are those wherein:

R_5 is $-C(O)-R_7$ or $-C(O)C(O)-R_7$;

each R_4 is a C_{1-5} straight or branched alkyl group optionally substituted with Ar;

m is 1;

n is 1;

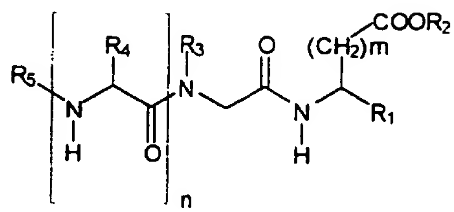
R_3 is $-CH_2Ar$ or 

E is CH or N;

each D is independently N or C, wherein C is optionally substituted with $-OR_{14}$, -F, -Cl, -Br, -I, $-NO_2$, $-S(O)_2-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

each R_9 and R_{10} is independently selected from the group consisting of -H, -Ar, and a $-C_{1-5}$ straight or branched alkyl group optionally substituted with -Ar.

The ICE inhibitors of another embodiment of this invention are those of formula (β):

β 

wherein:

m is 1 or 2;

n is 0, 1, or 2;

R_1 is selected from the group consisting of:
-CN,
-C(O)-H,
-C(O)-CH_2XR_6,
-C(O)-CH_2F,
-C=N-O-R_7, and
-C(O)-R_8;

X is selected from the group consisting of O, S, S(O), and $S(O)_2$;

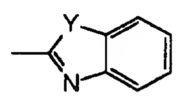
R_6 is independently selected from the group consisting of:
-H,
-$(CH_2)_p$-Ar, and
-C(O)-Ar;

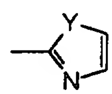
p is 0, 1, 2, or 3;

R_7 is selected from the group consisting of -Ar, a

$-C_{1-6}$ straight or branched alkyl group optionally substituted with -Ar, a $-C_{1-6}$ straight or branched alkenyl group optionally substituted with Ar, and a $-C_{2-6}$ straight or branched alkynyl group optionally substituted with Ar;

R_8 is selected from the following group, in which any ring may optionally be singly or multiply substituted by $-NH_2$, -C(O)-OH, -F, -Cl, -Br, -I, -OH, $-NO_2$, -CN, -perfluoroalkyl C_{1-3} alkyl, $-R_5$, $-OR_5$, $-OR_7$, $-N(H)-R_5$, $-N(H)-R_7$, 1,2-methylenedioxy, and $-SR_7$:

(hh)  ; and

(ii)  ;

wherein Y is independently selected from the group consisting of O and S;

each Ar is a cyclic group independently selected from the set consisting of a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl and a heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyraxolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl,

benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, peridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl, and the cyclic group is optionally being singly or multiply substituted with $-OR_{14}$, -F, -Cl, -Br, -I, $-NO_2$, $-S(O)_2-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

each R_9 and R_{10} are independently selected from the group consisting of -H, -Ar, and a $-C_{1-5}$ straight or branched alkyl group optionally substituted with Ar;

each R_{14} is -H or a C_{1-6} straight or branched alkyl group;

R_5 is selected from the group consisting of:

$-C(O)-R_7$,

$-C(O)-OR_9$,

$-C(O)-N(R_9)(R_{10})$,

$-S(O)_2-R_7$,

$-C(O)C(O)-R_7$,

$-R_7$, and

-H;

R_4 is a $-C_{1-5}$ straight or branched alkyl group optionally substituted with Ar or W;

W is $-OR_9$, $-SR_9$, $-N(H)C(NR_9)N(R_9)(R_{10})$, $-C(O)-OR_9$, and $-NR_9,(R_{10})$;

R_3 is $-CH_2Ar$ or a 5 to 15-membered non-aromatic cyclic group which contains between 1 and 3 rings, and which optionally contains between 0 and 2 endocyclic oxygen atoms, sulfur atoms, or nitrogen atoms, and wherein the cyclic group is optionally fused with Ar;

R_2 is -H, or a C_{1-6} straight or branched alkyl group, wherein the alkyl group is optionally substituted with Ar, -OH, $-OR_7$, -C(O)-OH, $C(O)-NH_2$, or $-OR_5$;

provided that when -Ar is substituted with a group containing R_9 or R_{10} which comprises one or more addditional -Ar groups, the -Ar groups are not substituted with a group containing R_9 or R_{10};

Preferred compounds of this embodiment are those wherein:

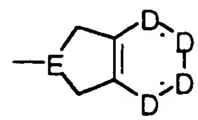
R_1 is -C(O)-H;

R_5 is $-C(O)-R_7$ or $-C(O)C(O)-R_7$;

R_4 is a $-C_{1-5}$ straight or branched alkyl group optionally substituted by -Ar;

m is 1;

n is 1;

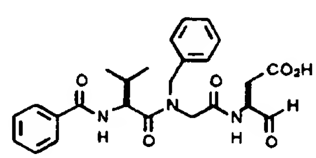
R_3 is $-CH_2Ar$, or 

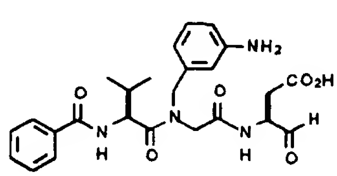
E is CH or N;

each D is independently N or C, wherein C is optionally substituted with $-OR_{14}$, -F, -Cl, -Br, -I, $-NO_2$, $-S(O)_2-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

each R_9 and R_{10} is independently selected from the group consisting of -H, -Ar, and a $-C_{1-5}$ straight or branched alkyl group optionally substituted with -Ar.

Preferred compounds of this embodiment include but are not limited to:

706 

737 

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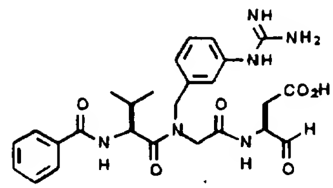

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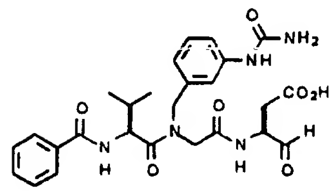

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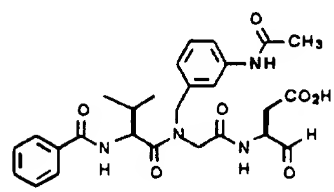

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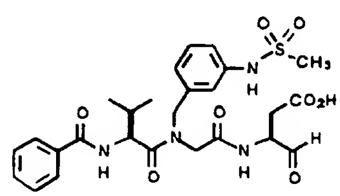

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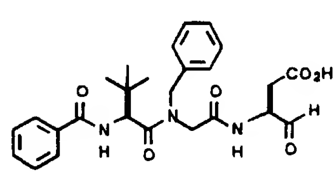

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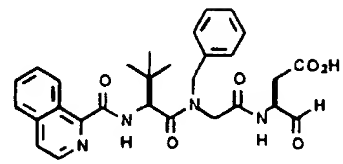

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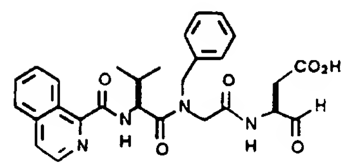

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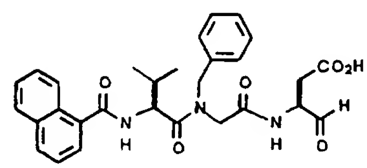

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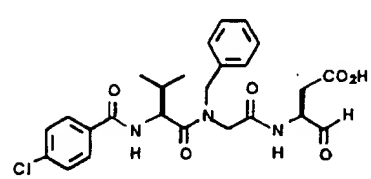

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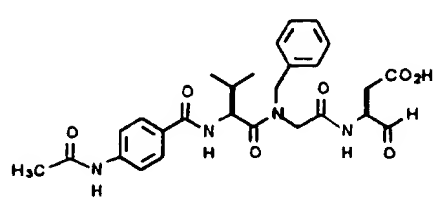

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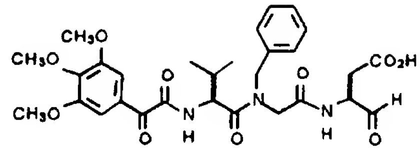

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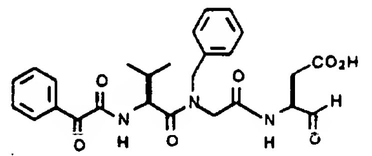

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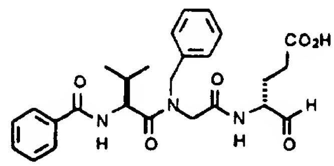

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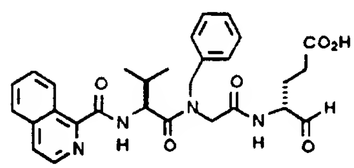

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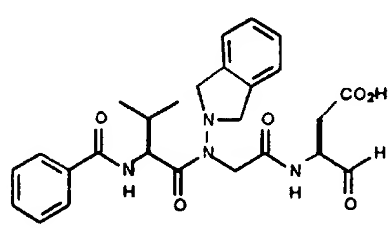

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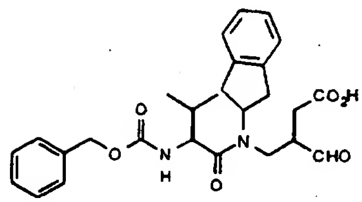


Other preferred compounds of this embodiment are those wherein:

R_1 is $-C(O)-R_8$;

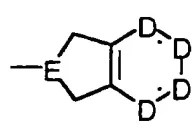
R_5 is $-C(O)-R_7$ or $-C(O)C(O)-R_7$;

R_4 is a $-C_{1-5}$ straight or branched alkyl group optionally substituted by -Ar;

m is 1;

n is 1;

R_3 is $-CH_2Ar$, or



E is CH or N;

each D is independently N or C, wherein C is optionally substituted with $-OR_{14}$, -F, -Cl, -Br, -I, $-NO_2$, $-S(O)_2-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

each R_9 and R_{10} is independently selected from the group consisting of -H, -Ar, and a $-C_{1-5}$ straight or branched alkyl group optionally substituted with -Ar.

Preferred compounds of this embodiment include but are not limited to:

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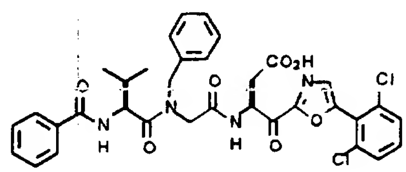

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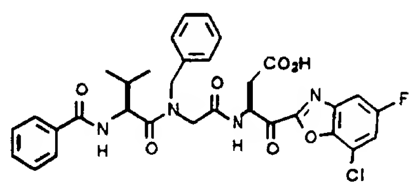

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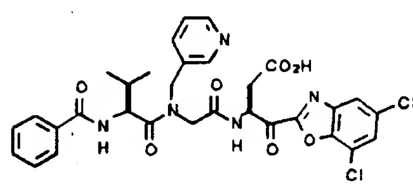

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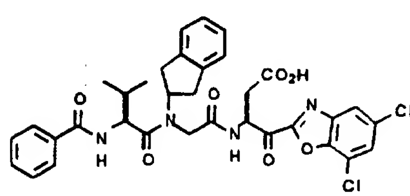

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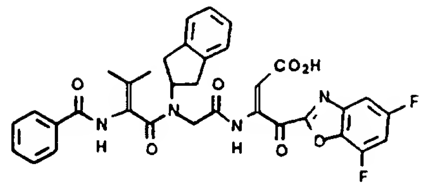

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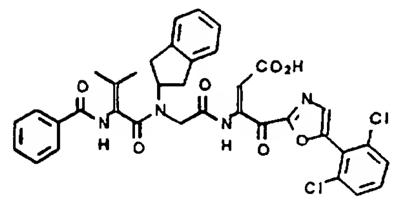

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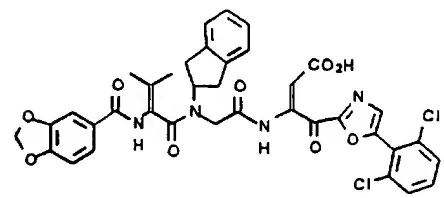

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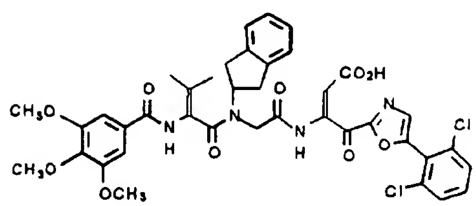

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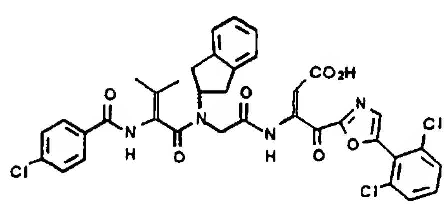


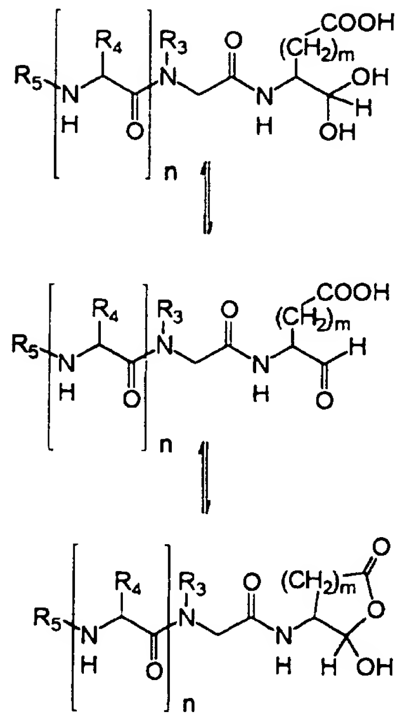
Other preferred compounds of this embodiment are those wherein R_1 is $-C(O)-CH_2XR_6$.

The ICE inhibitors of this invention may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

The compounds of this invention are among the most readily synthesized ICE inhibitors known. Previously described ICE inhibitors often contain four or more chiral centers and numerous peptide linkages. The relative ease with which the compounds of this invention can be synthesized represents an advantage in the large scale production of these compounds.

It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of solvent, pH, and others known to the practitioner skilled in the art. All such forms of these compounds are expressly included in the present invention. In particular, many of the compounds of this invention, especially those which contain aldehyde or ketone groups in R_1 and carboxylic acid groups (R_2=H), may take hemi-ketal (or hemi-acetal) or hydrated forms. For example, when R_1 is -(CO)-H and R_2 is -H compounds of this invention may take the forms depicted below:

Hydrated Form

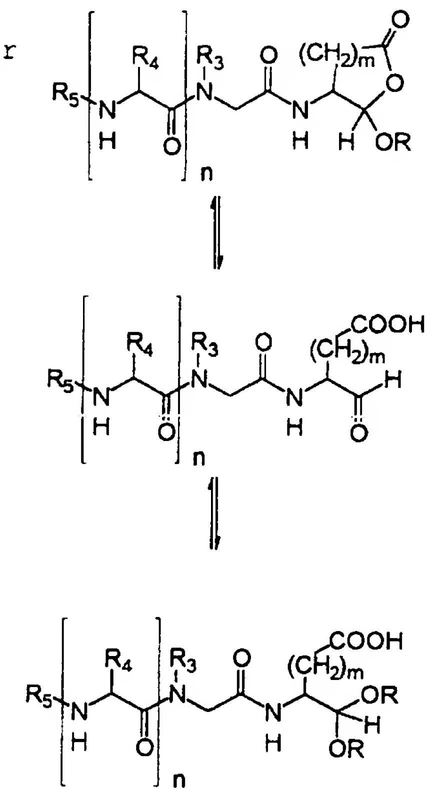


Hemi-ketal or Hemi-acetal Form

Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take acyloxy ketal, acyloxy acetal, ketal or acetal form:

Acyloxy Ketal or Acyloxy Acetal Form

Ketal or Acetal Form



In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these compounds are expressly included in the present invention.

It should be understood that the compounds of this invention may be modified by appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. In addition, the compounds may be

altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Such pro-drug forms typically demonstrate little or no activity in *in vitro* assays. Some examples of pro-drug forms include ketal, acetal, oxime, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the R_1 group of the compounds of this invention. Other examples of pro-drug forms include the hemi-ketal, hemi-acetal, acyloxy ketal, acyloxy acetal, ketal, and acetal forms that are described in EQ1 and EQ2.

The compounds of this invention are excellent ligands for ICE. Accordingly, these compounds are capable of targeting and inhibiting events in IL-1- and apoptosis-mediated diseases and, thus, the ultimate activity of that protein in inflammatory diseases, autoimmune diseases, proliferative disorders, infectious diseases, and degenerative diseases. For example, the compounds of this invention inhibit the conversion of precursor IL-1β to mature IL-1β by inhibiting ICE. Because ICE is essential for the production of mature IL-1β, inhibition of that enzyme effectively blocks initiation of IL-1 mediated physiological effects and symptoms, such as inflammation, by inhibiting the production of mature IL-1. Thus, by inhibiting IL-1β precursor activity, the compounds of this invention effectively function as IL-1 inhibitors.

The compounds of this invention may be employed in a conventional manner for the treatment of diseases which are mediated by IL-1 or apoptosis. Such

methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from an IL-1- or apoptosis-mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against IL-1- or apoptosis-mediated diseases over extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of ICE inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period time against IL-1- or apoptosis-mediated diseases.

The compounds of this invention may also be co-administered with other ICE inhibitors to increase the effect of therapy or prophylaxis against various IL-1- or apoptosis-mediated diseases.

In addition, the compounds of this invention may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxygenase inhibitors and antagonists of cytokines other than IL-1β.

The compounds of this invention can also be

administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO) or with prostaglandins, to prevent or combat IL-1- or apoptosis-mediated disease symptoms such as inflammation.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention may be comprised of a combination of an ICE inhibitor of this invention and another therapeutic or prophylactic agent.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene

glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride

derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical

compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about 0.01 and about

100 mg/kg body weight per day, preferably between about 1 and 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of IL-1- and apoptosis-mediated diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs. host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, and neurological damage due to stroke. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about

95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency o administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence or disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, and the patient's disposition to the disease and the judgment of the treating physician.

The IL-1 or apoptosis-mediated diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, inflammatory diseases, autoimmune diseases, proliferative disorders, infectious diseases, degenerative, and necrotic diseases.

Inflammatory diseases which may be treated or prevented include, but are not limited to osteoarthritis, acute pancreatitis, chronic

pancreatitis, asthma, and adult respiratory distress syndrome. Preferably, the inflammatory disease is osteoarthritis or acute pancreatitis.

Autoimmune diseases which may be treated or prevented include, but are not limited to, glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, and graft vs. host disease. Preferably, the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or psoriasis.

Bone destructive disorders which may be treated or prevented include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

Proliferative diseases which may be treated or prevented include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Infectious diseases which may be treated or prevented include, but are not limited to, sepsis, septic shock, and Shigellosis.

The IL-1-mediated degenerative or necrotic diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia.

Preferably, the degenerative disease is Alzheimer's disease.

The apoptosis-mediated degenerative diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1 and apoptosis-mediated diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to ICE or other cysteine proteases. As commercial reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide in biochemical or cellular assays for ICE and ICE homologs or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill in the art.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

Example 1

Inhibition of ICE

We obtained inhibition constants (K_i) and IC_{50} values for several compounds of this invention using the three methods described below:

1. Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-pNitroanilide substrate. Synthesis of analogous substrates is described by L. A. Reiter (Int. J. Peptide Protein Res. 43, 87-96 (1994)). The assay mixture contains:

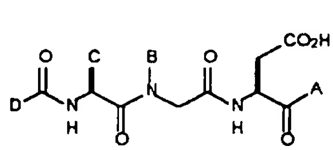
65 µl buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS @pH 8.1)
10 µl ICE (50 nM final concentration to give a rate of ~1mOD/min)
5 µl DMSO/Inhibitor mixture
20 µl 400µM Substrate (80 µM final concentration)
100µl total reaction volume

The visible ICE assay is run in a 96-well microtiter plate. Buffer, ICE and DMSO (if inhibitor is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader is set to incubate at 37 °C. After the 15 minute incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore (pNA) at 405 - 603 nm at 37 °C for 20 minutes. A linear fit of the data is performed and the rate is calculated in mOD/min. DMSO is only present during experiments involving inhibitors, buffer

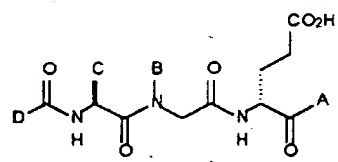
is used to make up the volume to 100 µl in the other experiments.

Example 2

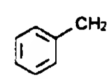
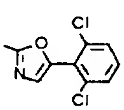
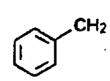
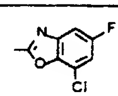
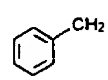
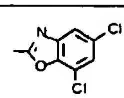
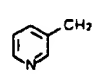
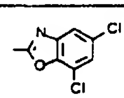
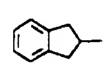
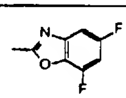
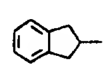
The following K_i values were determined for compounds 706, 710, 719, 720, 725-727, 729, 731, 733, 743, 745, and 747-757 using the assay described in Example 1. The structures of the compounds of Example 2 are shown in the following Table and in Example 3.

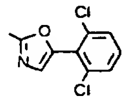
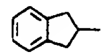
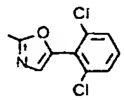
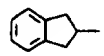
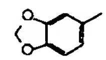
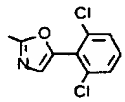
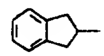
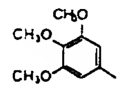
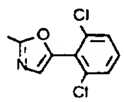
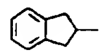
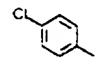
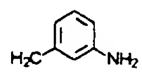
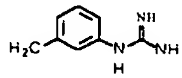
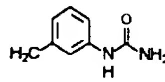
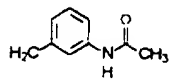
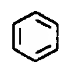
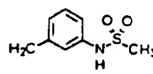
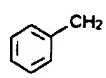
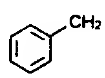
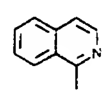
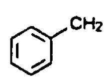
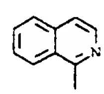
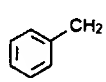
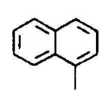
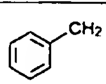
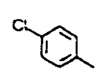


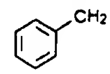
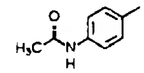
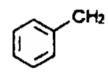
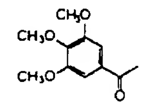
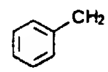
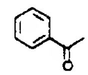
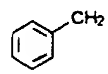
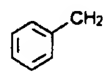
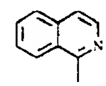
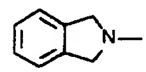
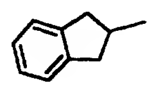
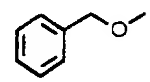
Type 1



Type 2

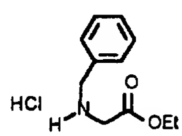
Cpd	Type	A	B	C	D	K_i (nM)
706	1	H		i-Pr		69
710	1			i-Pr		20
719	1			i-Pr		20
720	1			i-Pr		33
725	1			i-Pr		1.9
726	1			i-Pr		15

727	1			i-Pr		9.0
729	1			i-Pr		4.7
731	1			i-Pr		26
733	1			i-Pr		7.5
737	1	H		i-Pr		
739	1	H		i-Pr		
741	1	H		i-Pr		
743	1	H		i-Pr		60
745	1	H		i-Pr		45
746	1	H		t-Bu		
747	1	H		t-Bu		24
748	1	H		i-Pr		6
749	1	H		i-Pr		7
750	1	H		i-Pr		90

751	1	H		i-Pr		71
752	1	H		i-Pr		62
753	1	H		i-Pr		53
754	2	H		i-Pr		2500
755	2	H		i-Pr		390
756	1	H		i-Pr		
757	1	H		i-Pr		170

<u>Example 3</u>

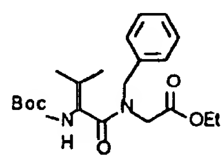
Compounds of Example 2 were synthesized as follows:



701

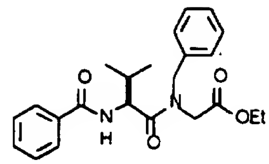
N-Benzylglycine Ethyl Ester (**701**): To a solution of benzaldehyde (14.0 g, 0.132 mol) in absolute EtOH (500 mL) was added glycine ethyl ester hydrochloride (37.0 g, 0.256 mol), NaOAc (32.5 g, 0.396 mol) and sodium cyanoborohydride (9.8 g, 0.158 mol), and the resulting mixture heated to reflux. After 1 hr at reflux, the

reaction was cooled and concentrated *in vacuo*. The residue was taken up into 1N NaOH and EtOAc. The layers were separated and the organic phase was washed with 1N NaOH, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken up into EtOAc (150 mL) and treated with gaseous HCl. The resulting solid was collected, washed with Et_2O and dried to provide 23.4 g of compound **701** as the HCl salt.



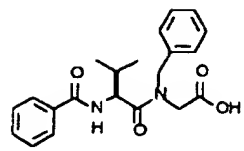
702

((2(*S*)-tert-Butoxycarbonylamino-3-methylbutyryl)benzyl-amino)acetic Acid Ethyl Ester (**702**): To a solution of N-Boc-valine (2.18 g, 10 mmol) and DIEA (4.4 mL, 25.3 mmol) in CH_2Cl_2 (20 mL) at -20 °C was added trimethylacetyl chloride (1.2 mL, 9.7 mmol). After stirring for 30 min, compound **701** (2.18 g, 10 mmol) was added and the reaction allowed to warm to rt and stir for 5 hr. The reaction was concentrated *in vacuo* and the residue taken up into EtOAc and H_2O. The layers were separated and the organic phase washed with sat. aq. $NaHCO_3$, sat. aq. $KHSO_4$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide 3.45 g of compound **702**.



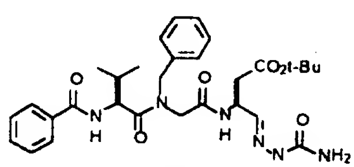
703

((2(*S*)-Benzoylamino-3-methylbutyryl)benzylamino)acetic Acid Ethyl Ester (**703**): To a solution of compound **702** (3.45 g, 8.8 mmol) in EtOAc at 0 °C was bubbled in gaseous HCl until saturated. The reaction was warmed to rt and stirred for 3 hr. Nitrogen was bubbled through the reaction to remove excess HCl, followed by concentration *in vacuo*. The residue suspended in CH_2Cl_2 (50 mL), treated with DIEA (3.4 mL, 19.5 mmol) followed by benzoyl chloride (1.2 mL, 10.3 mmol) and the reaction allowed to stir overnight. The reaction was concentrated *in vacuo* and the residue taken up into EtOAc and H_2O. The layers were separated and the organic phase washed with sat. aq. $NaHCO_3$, sat. aq. $KHSO_4$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide 3.45 g of compound **703**.



704

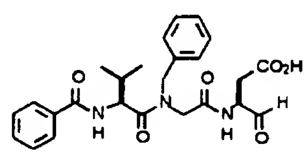
((2(*S*)-Benzoylamino-3-methylbutyryl)benzylamino)acetic Acid (**704**): To a solution of compound **703** (3.45 g, 8.8 mmol) in MeOH (9 mL) was added 1N LiOH (9 mL) and the reaction allowed to stir over night. The reaction was concentrated *in vacuo* and the residue taken up into EtOAc and H_2O. The layers were separated and the aqueous phase was acidified with 1N HCl. The product was extracted with EtOAc (2x). The extracts were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide 3.0 g of compound **704**.



705

3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl)benzyl-amino)acetylamino)-4-oxo-butyric Acid tert-Butyl Ester Semicarbazone (**705**): To a solution of 3(*S*)-(1-fluorenylmethyloxycarbonylamino)-4-oxobutyric acid tert-butyl ester semicarbazone (678 mg, 1.5 mmol; Prepared in a similar manner to the benzyloxycarbonyl analog in Graybill et al., Int. J. Protein Res., 44, pp. 173-82 (1994)) in acetonitrile (5.0 mL) was added diethylamine (780 μL, 7.5 mmol) and the reaction

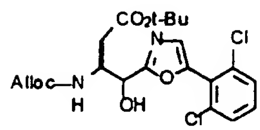
allowed to stir at rt for 1 hr. The reaction was concentrated *in vacuo* and the residue co-concentrated with toluene (3x) *in vacuo*. To a suspension of the residue, compound **704** (555 mg, 1.5 mmol) and HOBT (224 mg, 1.66 mmol) in 1:1 CH_2Cl_2:DMF (10 mL) at 0 °C, was added EDC (318 mg, 1.66 mmol). The reaction was warmed to rt and stirred over night. The reaction was diluted with EtOAc and H_2O. The layers were separated and the organic phase washed with sat. aq. $NaHCO_3$, sat. aq. $KHSO_4$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (elution with 2-6% MeOH:CH_2Cl_2) provided 600 mg of compound **705**.



706

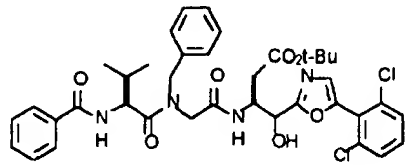
3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl) benzylamino)acetylamino)-4-oxo-butyric Acid (**706**): To a suspension of compound **705** (600 mg, 1.04 mmol) in CH_2Cl_2 (10 mL) was added TFA (4.0 mL) and the reaction allowed to stir for 4 hr. The reaction was concentrated *in vacuo* and the residue co-concentrated with toluene (3x). The residue was dissolved in MeOH (10 mL) and treated with HOAc (2.0 mL) followed by formaldehyde (2.0 mL). After stirring for 3 hr at rt, the reaction was concentrated *in vacuo*. Prep-HPLC provided 89 mg of compound **706**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.34 - 8.21 (m), 7.80 - 7.69 (m), 7.51 - 7.02 (m), 4.99 - 4.81 (m), 4.73 - 4.59 (m), 4.57 - 4.56 (m),

4.35 - 4.12 (m), 4.07 - 3.96 (m), 3.93 - 3.84 (m), 2.64 - 2.51 (m), 2.49 - 2.31 (m), 2.29 - 2.13 (m), 1.02 - 0.80 (m).



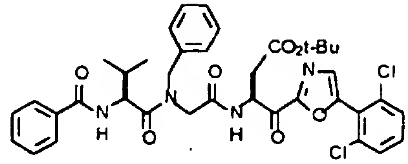
707

3(*S*)-(Allyloxycarbonyl)-amino-4-((2,6-dichloro-phenyl)-oxazol-2-yl)-4-hydroxy-butyric Acid tert-Butyl Ester (**707**). A solution of 5-(2,6-Dichloro-phenyl)oxazole (2.71g, 12.7 mmol; prepared by a similar method described in Tet. Lett. 2369 (1972)) in THF (65 mL) was cooled to -78 °C under a nitrogen atmosphere. To this solution was added n- butyl lithium (1.5M solution in hexane, 8.5 mL, 13.3 mmol). After 30 min. Magnesium bromide etherate (3.6 g, 13.9 mmol) was added and the solution was allowed to warm to -45 °C for 15 min. The reaction was cooled to -78 °C and 3(*S*)-(1-allyloxycarbonylamino)-4-oxobutyric acid tert-butyl ester (3.26g, 12.7 mmol; Graybill et al., Int. J. Protein Res., 44, 173-182 (1993)) in THF (65 mL) was added dropwise. The reaction was stirred for 25 min., then allowed to warm to -40 °C and stirred for 3h, and then at rt for 1h. The reaction was quenched with 5% $NaHCO_3$ (12 mL) and stirred for 3h. The THF was removed *in vacuo* and the resulting residue was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield 6.14 g. Purification gave 4.79 g of compound **707**.



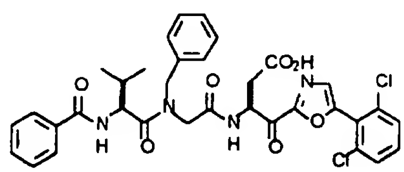
708

3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl)benzyl-amino)acetylamino)-4-(4-(2,6-dichlorophenyl)-oxazol-2-yl)-4-hydroxybutyric Acid tert-Butyl Ester (**708**): To a suspension of compound **704** (318 mg, 0.86 mmol) and compound **707** (370 mg, 0.78 mmol) in 1:1 CH_2Cl_2:DMF (8.0 mL) was added bis(triphenylphosphine) palladium dichloride (10 mg), followed by the dropwise addition of tri-n-butyl tin hydride (320 µL, 1.19 mmol). After the addition was complete, HOBT (212 mg, 1.57 mmol) was added and the reaction was cooled to 0 °C. added EDC (180 mg, 0.94 mmol) was added and the reaction allowed to warm to rt and stir overnight. The reaction was concentrated *in vacuo* and the residue taken up into EtOAc and sat. aq. $KHSO_4$. The layers were separated and the organic phase was washed with sat. aq. K_2CO_3, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel (elution with 2% MeOH:CH_2Cl_2) provided 150 mg of compound **708**.



709

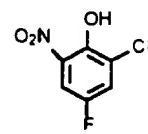
3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl) benzylamino)acetylamino)-4-(4-(2,6-dichlorophenyl)-oxazol-2-yl)-4-oxobutyric Acid tert-Butyl Ester (**709**): To a suspension of Dessmarten (259 mg, 0.61 mmol) in CH_2Cl_2 (4.0 mL) was added dropwise a solution of compound **708** (150 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL). After stirring at rt for 1hr. the reaction was concentrated *in vacuo*. The residue was dissolved into EtOAc and washed with 1:1 sat. aq. $Na_2S_2O_3$:sat. aq. $NaHCO_3$, sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel (elution with 2-5% MeOH: CH_2Cl_2) provided 74 mg of compound **709**.



710

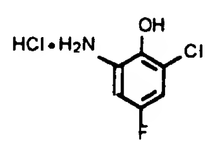
3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl) benzylamino)acetylamino)-4-(4-(2,6-dichlorophenyl)-oxazol-2-yl)-4-oxobutyric Acid (**710**): To a solution of compound **709** in CH_2Cl_2 (4.0 mL) was added TFA (2.0 mL) and the reaction stirred at rt for 1 hr. The reaction was concentrated *in vacuo* and the residue co-concentrated with toluene. Prep- HPLC provided 35

mg of compound **710**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.90 (m), 8.52 (m), 8.35 (m), 7.83 (m), 7.62 - 7.39 (m), 7.38 - 7.16 (m), 5.52 (m), 5.01 (m), 5.01 (m), 4.99 - 4.53 (m), 4.42 (m), 4.33 - 3.82 (m), 3.16 - 2.93 (m), 2.91 - 2.48 (m), 2.24 (m), 1.09 - 0.85 (m).



711

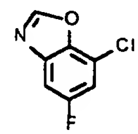
2-Chloro-4-fluoro-6-nitrophenol (**711**): To a mixture of 2-Chloro-4-fluorophenol (25 g, 0.171 mol) in H_2O (100 mL) and Et_2O (300 mL) at 0 °C was added dropwise concentrated nitric acid (25 mL). After the addition was complete the reaction was warmed to rt and stirred for 3 hr. The layers were separated and the organic phase washed with 1:1 brine:H_2O, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to a slurry. The slurry was diluted with hexane and the yellow solid collected and dried to provide 23.6 g of compound **711**.



712

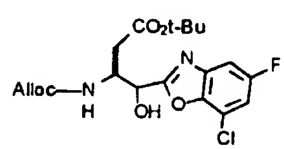
2-Chloro-4-fluoro-6-aminophenol Hydrochloride (**712**): A mixture of compound **711** (23.4 g, 0.122 mol) and platinum oxide (2.3 g) in absolute EtOH (120 mL) was placed under 1 atm of hydrogen and stirred until complete reduction had occurred. The hydrogen was replaced with nitrogen and the reaction was filtered

through Celite. The filtrate was diluted with Et_2O (300 mL) and gaseous hydrochloric acid was bubbled through the solution to provide a white precipitate. The solid was collected and dried under vacuum to provide 17.1 g of compound **712** as a white solid.



713

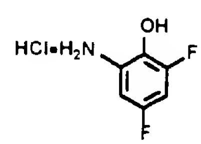
6-Chloro-4-fluorobenzoxazole (**713**): A mixture of compound **712** (17.0 g, 86.3 mmol) and trimethylorthoformate (18.9 mL, 0.173 mol) in absolute MeOH (90 mL) was heated to reflux upon which a solution formed. After stirring at reflux for 24 hr, the reaction was cooled and concentrated to provide an orange solid. The solid was dissolved into Et_2O, washed with 1N NaOH, brine, dried over $MgSO_4$, filtered and concentrated to provide a yellow orange solid. Recyrstallization from hot aqueous EtOH with rapid cooling and filtration provided 10.0 g of compound **713** as white needles. Note that prolong standing in aqueous EtOH causes decomposition of compound **713**.



714

3(*S*)-(Allyloxycarbonyl)-amino-4-(6-chloro-4-fluorobenzoxazol-2-yl)-4-hydroxy-butyric Acid tert-Butyl Ester (**714**). To a solution compound **713**

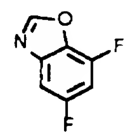
(2.06 g, 12.0 mmol) in THF (24 mL) at -78 °C was added dropwise butyl lithium (1.6 M in hexane, 7.0 mL, 12.1 mmol) and the reaction allowed to stir for 1 hr. The reaction was treated with solution of magnesium bromide (1M in benzene:Et_2O 1:4, 13.2 mL) and the reaction warmed to -40 °C. After stirring for 1 hr, the reaction was cooled to -78 °C and treated with a solution of 3(*S*)-(1-allyloxycarbonylamino)-4-oxobutyric acid tert-butyl ester (2.57 g, 10 mmol) in THF (12 mL). The reaction was allowed to slowly warm to rt and stir overnight. The reaction was quenched with sat. aq. NH_4Cl, diluted with EtOAc and enough H_2O added to make the aqueous phase clear. The layers were separated and the organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (elution with 15-45% EtOAc:hexane) provided 2.0 g of compound **714**.



715

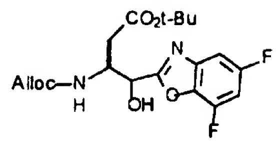
2,4-Difluoro-6-aminophenol Hydrochloride (**715**): A mixture of 2,4-Difluoro-6-nitrophenol (28.4 g, 0.162 mol; prepared by a similar method as **711** except replacing 2-chloro-4-fluorophenol with 2,4-difluorophenol) and 10% palladium on carbon (3.5 g) in absolute MeOH (120 mL) was placed under 1 atm of H_2 and stirred until complete reduction had occurred. The H_2 was replaced with nitrogen and the reaction was

filtered through Celite. Gaseous HCl was bubbled through the filtrate and the resulting solution concentrated. The residue was taken up into H_2O, washed with Et_2O (2x), neutralized with solid $NaHCO_3$ and the product extracted with Et_2O. The extracts were combined dried over $MgSO_4$ and filtered. The filtrate was treated with gaseous HCl and resulting precipitate collected and dried under vacuum to provide 12.9 g of compound **715** as a beige solid.



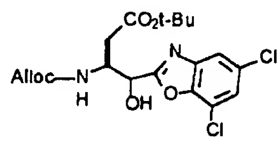
716

4,6-Difluorobenzoxazole (**716**): A mixture of compound **715** (12.8 g, 70.7 mmol) and trimethylorthoformate (23 mL, 0.212 mol) in absolute MeOH (90 mL) was heated to reflux upon which a solution formed. After stirring at reflux for 24 hr, the reaction was cooled and concentrated. The residue was dissolved into Et_2O, washed with 1N sodium hydroxide, brine, dried over $MgSO_4$, filtered and concentrated. Distillation under reduced pressure afforded 5.0 g of compound **716** as a clear liquid, which solidified upon standing.



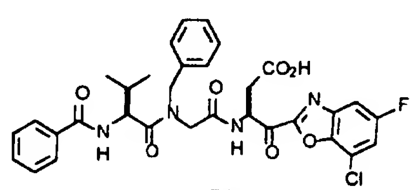
717

3(*S*)-(Allyloxycarbonyl)-amino-4-(4,6-difluorobenzoxazol-2-yl)-4-hydroxy-butyric Acid tert-Butyl Ester (**717**). compound **717** was prepared as described for compound **714**, except compound **713** was replaced with compound **716**.



718

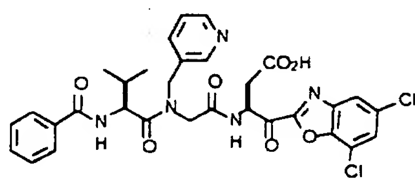
3(*S*)-(Allyloxycarbonyl)-amino-4-(4,6-dichorobenzoxazol-2-yl)-4-hydroxy-butyric Acid tert-Butyl Ester (**718**). compound **718** was prepared by a similar method as that used for compound **714**, except compound **711** was replaced with 2,4-dichloro-6-nitrophenol.



719

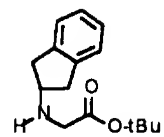
3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl)benzyl-amino)acetylamino)-4-(6-chloro-4-fluorobenzoxazol-2-yl)-4-oxobutyric Acid (**719**): Compound **719** was prepared by a method similar to the method used to prepare compound **710**, except compound **707** was replaced with compound **714**

in the preparation of **708**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.70 - 8.54 (m), 8.48 - 8.35 (m), 8.34 - 8.08 (m), 7.98 - 7.87 (m), 7 .75 - 7.67 (m), 7.63 (m), 7.58 (m), 7.51 - 7.44 (m), 7.43 - 7.29 (m), 7.28 - 7.03 (m), 6.97 (m), 5.51 (m), 4.99 - 4.66 (m), 4.65 - 4.26 (m), 4.25 - 3.61 (m), 3.42 (m), 3.13 - 2.83 (m), 2.68 - 2.42 (m), 2.23 - 2.00 (m), 1.02 - 0.69 (m).



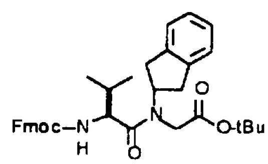
720

3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl)-3-picolylamino)acetyl-amino)-4-(4,6-dichlorobenzoxazol-2-yl)-4-oxobutyric Acid (**720**): Compound **720** was prepared by a method similar to the method used to prepare compound **710**, except replacing benzaldehyde with 3-pyridinecarboxaldehyde in the preparation of **701** and replacing compound **707** with compound **718** in the preparation of **708**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.88 - 8.44 (m), 8.42 - 8.20 (m), 7.91 - 7.58 (m), 7.55 - 7.30 (m), 5.51 (m), 4.72 - 4.11 (m), 3.92 - 3.52 (m), 3.26 - 2.92 (m), 2.72 -2.51 (m), 2.32 - 1.91 (m), 1.46 - 1.21 (m), 1.11-0.68 (m).



721

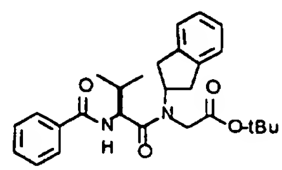
N-Indan-2-ylglycine t-Butyl Ester (**721**): To a suspension of 2-aminoindane hydrochloride (5.0g, 29.5 mmol) and powdered K_2CO_3 (8.3 g, 60.0 mmol) in absolute EtOH (30 mL) was added tert-butyl bromoacetate (4.4 mL, 29.5 mmol). After stirring for 10 min at rt the reaction was heated to 45 °C and stirred for 2 hr. The reaction was cooled to rt, diluted with EtOAc, filtered and concentrated. Chromatography of the residue on silica gel (elution with 20% EtOAc:hexane) provided 4.7g of compound **721** as a white crystalline solid.



722

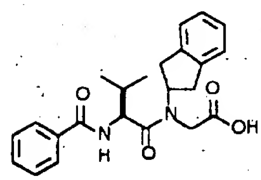
((2(*S*)-Fluorenylmethyloxycarbonylamino-3-methylbutyryl) indan-2-ylamino)acetic Acid t-Butyl Ester (**722**): To a partial solution of N-Fmoc-valine (9.08 g, 26.8 mmol) in CH_2Cl_2 (50 mL) containing DMF (100µ) was slowly added oxalyl chloride (3.5 mL, 40.2 mmol) upon which an evolution of gas occurred and a yellow solution formed. After stirring for 30 min, the reaction was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and treated with DIEA (2.3 mL, 13.4 mmol) followed by a solution of compound **721** (3.31 g, 13.4 mmol) in CH_2Cl_2. After stirring overnight, the

reaction was diluted with EtOAc, washed with 5% $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (elution with 10-20% EtOAc:hexane) provided 7.2 g of compound **722**.



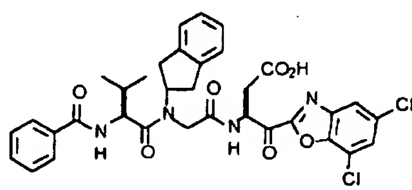
723

((2(*S*)-Benzoylamino-3-methylbutyryl)indan-2-ylamino)acetic Acid t-Butyl Ester (**723**): To a solution of compound **722** (500 mg, 0.88 mmol) in CH_3CN (6.0 mL) was added diethylamine (455μ, 4.4 mmol) and the reaction allowed to stir for 2 hr. The reaction was concentrated and the residue co-concentrated with toluene (2x) to provide a viscous oil. The residue was dissolved in CH_2Cl_2 (5 mL) containing DMF (2 mL), treated with benzoic acid (161 mg, 1.32 mmol) followed by EDC (252 mg, 1.32 mmol) and the reaction allowed to stir overnight. The reaction was diluted with EtOAc and washed with H_2O. The aqueous layer was re-extracted with EtOAc. The extracts were combined washed with 5% $KHSO_4$, filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (elution with 10% EtOAc:hexane) provided 240 mg of compound **723**.



724

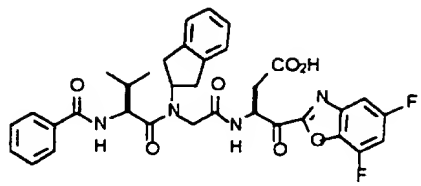
((2(*S*)-Benzoylamino-3-methylbutyryl)indan-2-ylamino)acetic Acid (24): To a solution of compound **723** (240 mg, 0.53 mmol) in CH_2Cl_2 (4.0 mL) was added TFA (2.0 mL) and the reaction stirred at rt for 1 hr. The reaction was concentrated *in vacuo* and the residue co-concentrated with toluene. The material was used directly in the next reaction without further purification.



725

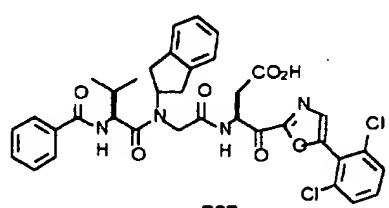
3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl)indan-2-ylamino)acetylamino)-4-(4,6-dichlorobenzoxazol-2-yl)-4-oxobutyric Acid (**725**): Compound **725** was prepared by a method similar to the method used to prepare compound **710**, except compound **704** was replaced with compound **724** and compound **707** was replaced with compound **718** in the preparation of compound **708**: ^1H NMR (500 MHz, CD_3OD) δ 8.7-8.6 (m), 8.6-8.4 (m), 8.1 (d), 8.0-7.8 (m), 7.6-7.5 (m), 7.5-7.4 (m), 7.2-7.0 (m), 7.0-6.9 (m), 5.5-5.3 (m), 5.3-5.2 (m), 4.6-4.5 (m), 4.5-4.3 (m), 4.2-4.0

(m), 3.8-3.6 (m), 3.3 (s), 3.2-3.1 (m), 3.1-3.0 (m), 3.0-2.8 (m), 2.7-2.6 (m), 2.4-2.0 (m), 1.2-0.6 (m).



726

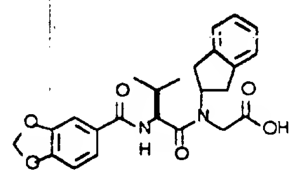
3(*S*)-(2-(2(*S*)-Benzoylamino-3-methylbutyryl)indan-2-ylamino)acetylamino)-4-(4,6-difluorobenzoxazol-2-yl)-4-oxobutyric Acid (**726**): Compound **726** was prepared by a method similar to the method used to prepare compound **710**, except compound **704** is replaced with compound **724** and compound **707** is replaced with compound **717** in the preparation of compound **708**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.7-8.6 (m), 8.6-8.4 (m), 8.1 (d), 8.0-7.8 (m), 7.6-7.5 (m), 7.5-7.4 (m), 7.2-7.0 (m), 7.0-6.9 (m), 5.5-5.3 (m), 5.3-5.2 (m), 4.6-4.5 (m), 4.5-4.3 (m), 4.2-4.0 (m), 3.8-3.6 (m), 3.3 (s), 3.2-3.1 (m), 3.1-3.0 (m), 3.0-2.8 (m), 2.7-2.6 (m), 2.4-2.0 (m), 1.2-0.6 (m).



727

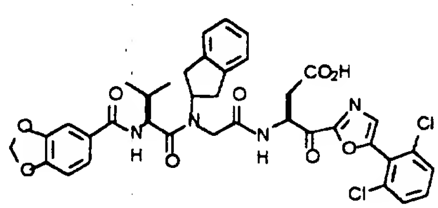
3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl)indan-2-ylamino)acetylamino)-4-(4-(3,5-dichlorophenyl)oxazol-2-yl)-4-oxobutyric Acid (**727**): Compound **727** was prepared by a method similar to the method use to prepare compound **710** , except compound **704** is replaced with

compound **724** in the preparation of compound **708**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (d), 8.38 - 8.21 (m), 8.20 - 8.11 (m), 7.81 - 7.72 (m), 7.50 - 7.32 (m), 7.14 - 6.93 (m), 5.52 - 5.40 (m), 5.22 - 5.13 (m), 5.08 (m), 4.96 (d), 4.56 (d), 4.48 - 4.37 (m), 4.21 - 4.10 (m), 3.98 (t), 3.82 (d), 3.26 - 3.11 (m), 3.10 - 2.88 (m), 2.25 - 2.12 (m), 1.04 - 0.83 (m).



728

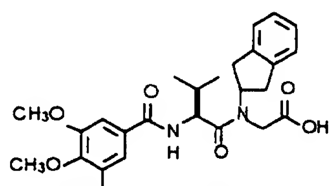
((2(*S*)-Benzo(1,3)dioxole-5-carbonylamino-3-methylbutyryl)indan-2-ylamino)acetic Acid (**728**): Compound **728** was prepared by a method similar to the method used to prepare compound **724**, except benzoic acid is replaced with piperonylic acid in the preparation of compound **723**.



729

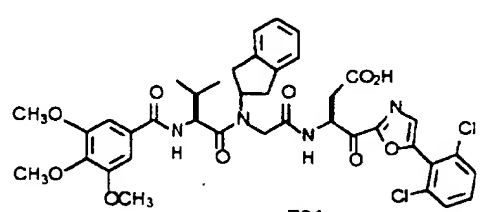
3(*S*)-(2-((2(*S*)-((Benzo(1,3)dioxole-5-carbonyl)amino)-3-methylbutyryl)indan-2-yl amino)acetylamino)-4-(4-(3,5-dichlorophenyl)oxazol-2-yl)-4-oxobutyric Acid (**729**): Compound **729** was prepared by a method similar to the

method used to prepare compound **710**, except compound **704** is replaced with compound **728** in the preparation of **708**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.36 (m), 8.22 - 8.03 (m), 7.58 - 7.37 (m), 7.36 - 7.23 (m), 7.22 - 7.01 (m), 6.89 (m), 6.00 (s), 5.51 (m), 5.29 - 5.04 (m), 4.97 (d), 4.61 - 4.49 (m), 4.48 - 4.31 (m), 4.27 - 4.19 (m), 4.09 - 3.78 (m), 3.28 - 3.19 (m), 3.18 - 2.93 (m), 2.90 - 2.59 (m), 2.51 (m), 2.22 (m), 1.12 - 0.83 (m).



730

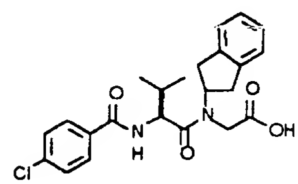
((2(*S*)-(3,4,5-Trimethoxybenzoylamino)-3-methylbutyryl) indan-2-ylamino)acetic Acid (**730**): Compound **730** was prepared by a method similar to the method used to prepare compound **724**, except benzoic acid is replaced with 3,4,5-trimethoxybenzoic acid in the preparation of **723**.



731

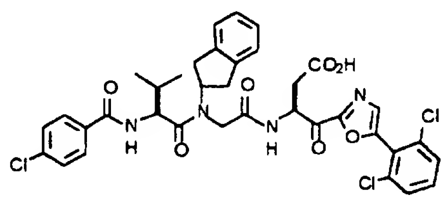
3(*S*)-(2-((2(*S*)-(3,4,5-Trimethoxybenzoylamino)-3-methylbutyryl)indan-2-yl amino)acetylamino)-4-(4-(3,5-dichlorophenyl)oxazol-2-yl)-4-oxobutyric Acid (**731**): Compound **731** was prepared by a method similar to the

method used to prepare compound **710**, except compound **704** is replaced with compound **730** in the preparation of **708**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.51 - 8.32 (m), 8.31 - 8.22 (m), 7.60 - 7.03 (m), 5.62 - 5.49 (m), 5.32 - 5.02 (m), 4.97 (m), 4.64 - 4.53 (m), 4.48 - 4.21 (m), 4.09 - 3.72 (m), 3.28 - 2.89 (m), 2.85 - 2.42 (m), 2.25 (m), 1.38 - 1.24 (m), 1.11 - 0.83 (m).



732

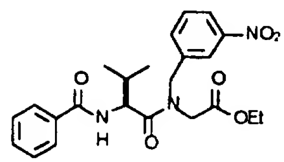
((2(*S*)-(3,4,5-Trimethoxybenzoylamino)-3-methylbutyryl) indan-2-ylamino)acetic Acid (**732**): Compound **732** was prepared by a method similar to the method used to prepare compound **724**, except benzoic acid is replaced with 4-chlorobenzoic acid in the preparation of **723**.



733

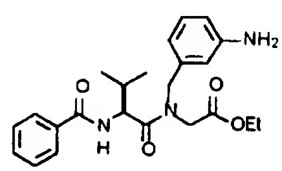
3(*S*)-(2-((2(*S*)-(4-Chlorobenzoylamino)-3-methylbutyryl) indan-2-yl amino)acetylamino)-4-(4-(3,5-dichlorophenyl)oxazol-2-yl)-4-oxobutyric Acid (**733**): Compound **33** was prepared by a method similar to the method used to prepare compound **710**, except compound **704** is replaced with compound **732** in the

preparation of **708**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.99, 6.4 - 6.2 (m), 5.8 - 6.0 (m), 5.7 - 5.4 (m), 4.0 - 3.9 (m), 3.7 - 3.6 (m), 3.6 - 3.5 (m), 3.5 - 3.4 (m), 3.4 - 3.2 (m), 3.0 (m), 2.8 (m), 2.7 (m), 2.5 - 2.3 (m), 1.8 - 1.6 (m), 1.3 - 1.6 (m), 1.2 (m), 0.6 (m).



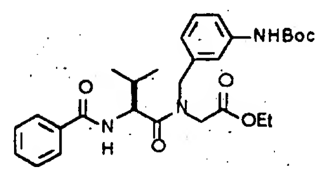
734

((2(*S*)-Benzoylamino-3-methylbutyryl)-(3-nitrobenzyl)amino)acetic Acid Ethyl Ester (**734**): Compound **734** was prepared by a method similar to the method used to prepare compound **703** except benzaldehdye was replaced with 3-nitrobenzaldehyde in the preparation of **701**.



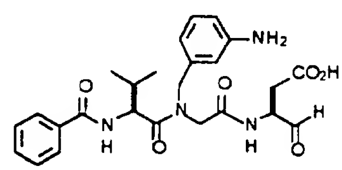
735

((2(*S*)-Benzoylamino-3-methylbutyryl)-(3-aminobenzyl)amino)acetic Acid Ethyl Ester (**735**): A mixture of compound **734** (1.5 g, 3.4 mmol) and 10% Pd/C (150 mg) in MeOH (35 mL) was placed under H_2 (1 atm) and stirred until the reduction was complete. The H_2 was replaced with nitrogen and the reaction filtered. The filtrate was concentrated to provide 1.38 g of compound **735**.



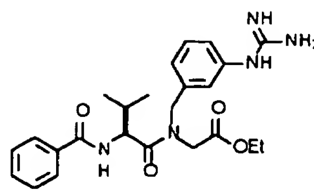
736

((2(*S*)-Benzoylamino-3-methylbutyryl)-(3-Bocaminobenzyl)amino)acetic Acid Ethyl Ester (**703**): To a solution of compound **735** (1.45 g, 3.5 mmol) and DIEA (740 µl, 4.25 mmol) in CH_2Cl_2 (7.0 mL) containing a catalytic amount of N,N-dimethylaminopyridine, was added di-tert-butyldicarbonate (850 mg, 3.9 mmol). After 1 hr, the reaction was diluted with EtOAc, washed with H_2O, sat. aq. $KHSO_4$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide 1.78 g of compound **736**.



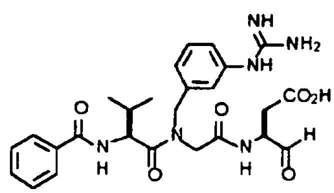
737

3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl)-(3-aminobenzyl)amino)acetylamino)-4-oxo-butyric Acid (**737**): Compound **737** was prepared by a method similar to the method used to prepare compound **706**, except compound **703** was replaced with compound **736**.



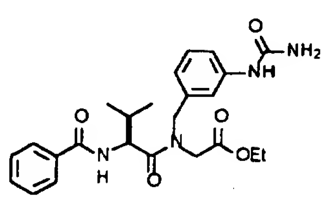
738

((2(*S*)-Benzoylamino-3-methylbutyryl)-(3-guanidionbenzyl)amino)acetic Acid Ethyl Ester (**738**): Compound **738** was prepared by a method similar to the method used to prepare compound **742**.



739

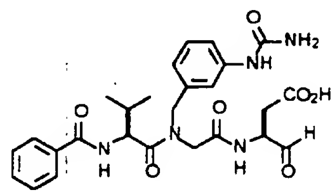
3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl)-(3-guanidionbenzyl)amino) acetylamino)-4-oxo-butyric Acid (**739**): Compound **739** was prepared by a method similar to the method used to prepare compound **706**, except compound **703** was replaced with compound **738**.



740

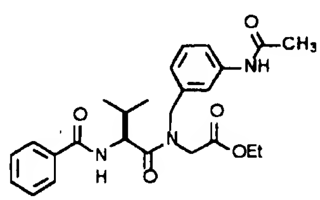
((2(*S*)-Benzoylamino-3-methylbutyryl)-(3-ureidobenzyl)amino)acetic Acid Ethyl Ester (**740**):

Compound **740** was prepared by method similar to the method used to prepare compound **742**.



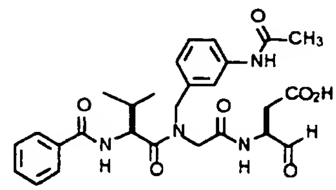
741

3(*S*)-(2-((2(*S*)-Benzoylamino-3-methylbutyryl)-(3-ureidobenzyl)amino)acetylamino)-4-oxo-butyric Acid (**741**): Compound **741** was prepared by a method similar to the method used to prepare compound **706**, except compound **703** was replaced with compound **740**.



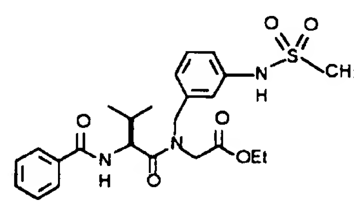
742

(3-Acetylaminobenzyl-(2(*S*)-benzoylamino-3-methylbutyryl)-amino)acetic Acid Ethyl Ester (**742**): To a solution of 735 (435.0 mg, 1.06 mmol) in pyridine (3.0 ml) was added acetic anhydride (50 µL, 1.59 mmol) and the reaction allowed to stir overnight. The reaction was diluted with EtOAc and 1N Hcl. The layers were separated and the organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness to provide 480 mg of **742**.



743

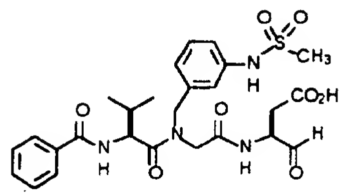
3(*S*)-(2-((3-Acetylaminobenzyl)-(2(*S*)-benzoylamino-3-methylbutyryl)amino)acetyl amino)-4-oxo-butyric Acid (**743**): Compound **743** was prepared by a method similar to the method used to prepare compound **706**, except compound **703** was replaced with compound **742**. ^{1}H NMR (CD_3OD) δ 8.31 - 8.27 (m), 7.82 - 7.73 (m), 7.51 - 7.36 (m), 7.28 - 7.13 (m), 6.99 (d), 6.91 (d), 4.96 - 4.69 (m), 4.66 - 4.46 (m), 4.37 - 4.28 (m), 4.11 - 3.98 (t), 3.97 - 3.89 (m), 3.31 - 3.19 (m), 2.67 - 2.52 (m), 2.48 - 2.32 (m), 2.0 (d), 1.01 - 0.86 (m).



744

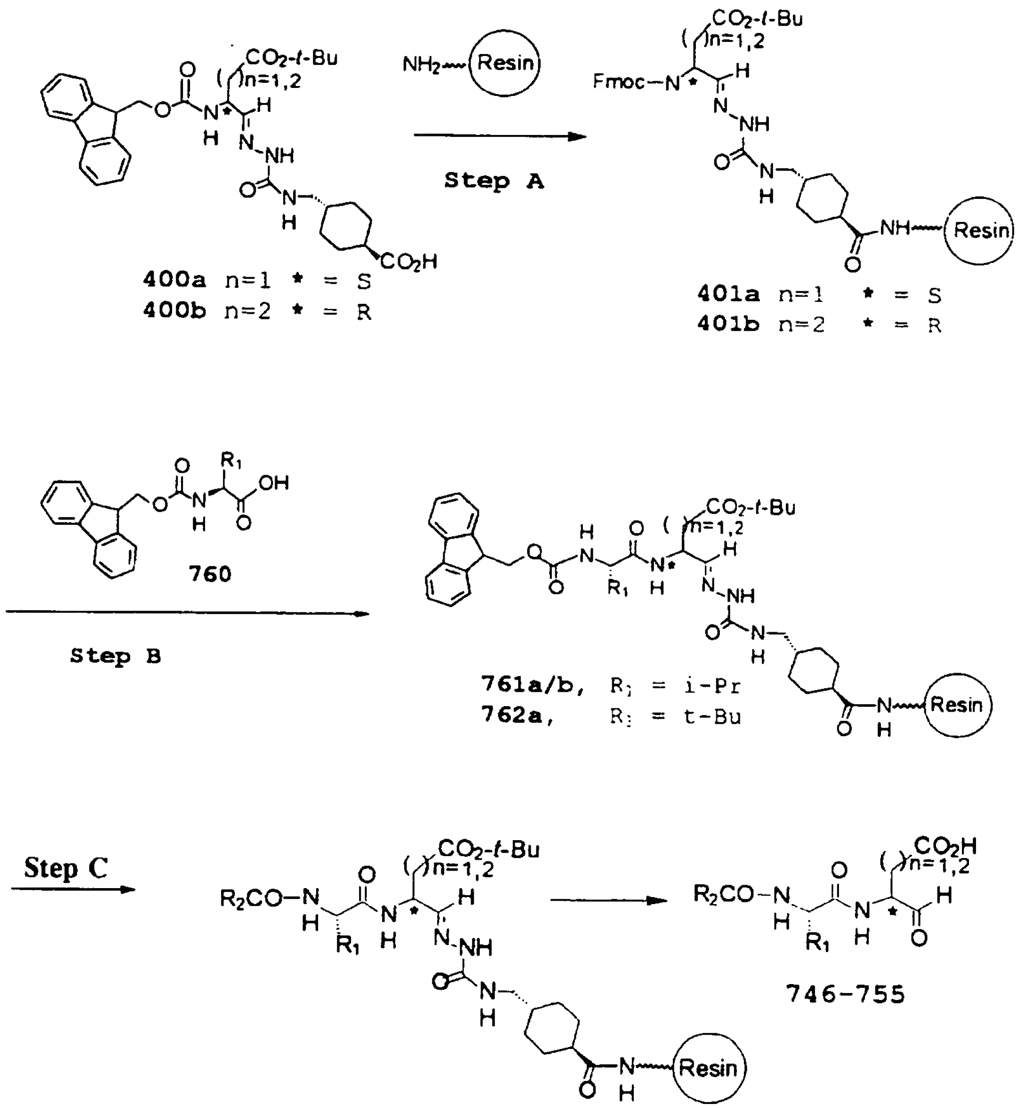
((2(*S*)-Benzoylamino-3-methylbutyryl)-(3-methanesulfonylbenzyl)amino)acetic Acid Ethyl Ester (**744**): To a solution of 735 (476.0 mg, 1.16 mmol) in pyridine (3.0 mL) was added methanesulfonyl chloride (135 µL, 1.75 mmol), and the reaction allowed to stir overnight. The reaction was diluted with EtOAc and 1N Hcl. The layers were separated and the organic phase

washed with brine, dried over $MgSO_4$, filtered and concentrated to provide 550 mg of **744**.



745

3(*S*)-(2-((2(*S*)-Benzoylamino-methylbutyryl)-(3-methanesulfonylbenzyl) amino)acetylamino)-4-oxo-butyric Acid (**745**): Compound **745** was prepared by a method similar to the method used to prepare compound **706**, except compound **703** was replaced with compound **744**. ^{1}H NMR (CD_3OD) δ 8.29 (m), 8.02 (m), 7.82 - 7.69 (m), 7.51 - 7.32 (m), 7.29 - 7.01 (m), 6.98 (d), 4.94 - 4.38 (m), 4.36 (d), 4.34 (d), 4.30 - 4.13 (m), 4.04 (d), 3.31 - 3.19 (m), 2.88 - 2.77 (m), 2.64 - 2.48 (m), 2.44 - 2.32 (m), 2.21 (m), 1.00 - 0.83 (m).



400a n=1 * = S
400b n=2 * = R

401a n=1 * = S
401b n=2 * = R

760

761a/b, R_1 = i-Pr
762a, R_1 = t-Bu

746-755

Step A. Synthesis of 401 a/b. TentaGel S® NH_2 resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with DMF (3 X 50 mL), 10% (v/v) DIEA in DMF (2 X 50 mL) and finally with DMF (4 X 50 mL). Sufficient DMF was added to the resin to obtain a slurry followed by **713a** (1.42 g, 2.4 mmol,

prepared from either (3S) 3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et al. J. Am. Chem. Soc., 114, 3156-3157 (1992)) or **713b** (1.42 g, 2.4 mmol, prepared from (3R) 3-(fluorenylmethyloxycarbonyl)-4-oxopentanoic acid t-butyl ester according to A.M. Murphy et al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), HOBT ($HOBT{\cdot}H_2O$; 0.367 g 2.4 mmol), O-benzotriazole-N,N,N,N'- tetramethyluronium hexafluorophosphate (HBTU; 0.91 g 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin was isolated on a sintered glass funnel by suction filtration and washed with DMF (3 X 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) acetic anhydride/DMF (2 X 25 mL) directly in the funnel (10 min/wash). The resin was washed with DMF (3 X 50 mL) and CH_2Cl_2 (3 X 50 mL) prior to drying overnight *in vacuo*.

Step B. Method 1: Synthesis of 761a/b and 762a. Resins **761a** and **762a** were prepared from resin **401a** (0.24 g, 0.038 mmol) and Fmoc-Valine or Fmoc-t-Leucine, respectively, while resin **761b** was prepared from resin **401b** and Fmoc-Valine using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with DMF (3 X 1 mL), deprotection with 25% (v/v) piperidine in DMF (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min. The resin was washed with DMF (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL). The resin was then acylated with a solution of either 0.4M Fmoc-1-Valine or Fmoc-t-Leucine and 0.4M HOBT in N-methypyrrolidone

(1 mL), a solution of 0.4M HBTU in N-methypyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at rt. The acylation step was repeated. Finally, the resins were washed with DMF (3 X 1 mL).

Step C. Method 1. Synthesis of 747, 748, 752, 753, and 755. The appropriate carboxylic acid (0.4 M in 0.4 M HOBt/NMP) was coupled to the resin as described in Step B. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H_2O (v/v, 1.5 mL) for 30 min at rt. After washing the resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 Et_2O:pentane (12 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% CH_3CN/90% H_2O/0.1% TFA (15 mL) and lyophilized to obtain the crude product as a white powder. The compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5 u, 21.4 X 250 mm) eluting with a linear CH_3CN gradient (10% - 60%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized.

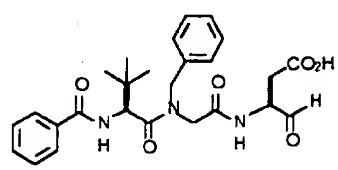
Step C. Method 1A. Synthesis of 751. Following a similar procedure as method 1, resin **761a** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described in Step C and the free amine was acetylated with 20% (v/v) acetic anhydride in DMF (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2 hr at rt. The

acetylation step was repeated. Cleavage of the aldehyde from the resin gave **751**.

Analytical HPLC methods:

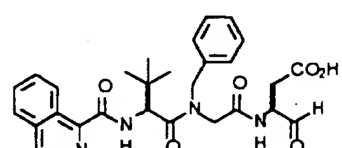
(1) Waters DeltaPak C18, 300A (5u, 3.9 X 150 mm). Linear CH_3CN gradient (10% - 60%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

Compounds **746-755** were prepared from the following combinatorial methods.



746

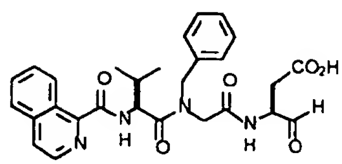
3(*S*)-(2-((2(*S*)-Benzoylamino-3,3-dimethylbutyryl)benzylamino)acetylamino)-4-oxo-butyric Acid (**746**): 0.7 mg (4%) as a white solid: Rt(1) = 11.14 min (87%); (M+H)+ = 482 ($C_{26}H_{31}N_3O_6$ requires 481.6).



747

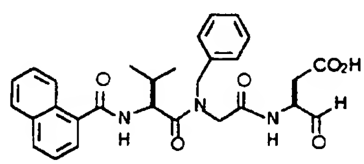
3(*S*)-(2(*S*)-(Benzyl-(2-((isoquinoline-1-carbonyl)amino)-3,3-dimethylbutyryl) amino)acetylamino)-4-oxo-butyric Acid (**747**): 2.0 mg (8%) as a white solid: Rt(1) =

12.27 min (98%); (M+H)+ = 533 ($C_{29}H_{32}N_4O_6$ requires 532.6).



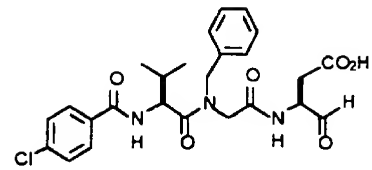
748

3(*S*)-(2(*S*)-(Benzyl-(2-((isoquinoline-1-carbonyl)amino)-3-methylbutyryl) amino)acetylamino)-4-oxo-butyric Acid (**748**): 9.2 mg (38%) as a white solid: Rt(1) = 11.05 min (98%); (M+H)+ = 519 ($C_{28}H_{30}N_4O_6$ requires 518.6).



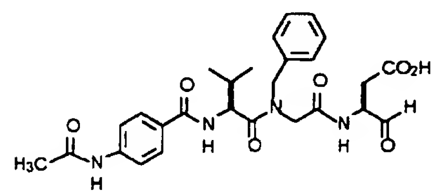
749

3(*S*)-(2(*S*)-(Benzyl-(2-((napthalene-1-carbonyl)amino)-3-methylbutyryl) amino)acetylamino)-4-oxo-butyric Acid (**749**): 7.9 mg (40%) as a white solid: Rt(1) = 11.78 min (98%); (M+H)+ = 518 ($C_{29}H_{31}N_3O_6$ requires 517.6).



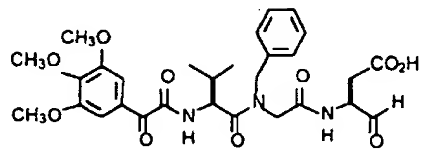
750

3(*S*)-(2-((2(*S*)-(4-Chlorobenzoyl)amino-3-methylbutyryl)benzylamino)acetylamino)-4-oxo-butyric Acid (**750**): 5.9 mg (31% as a white solid: Rt(1) = 11.63 min (98%); (M+H)+ = 502 ($C_{25}H_{28}C_1N_3O_6$ requires 501.5).



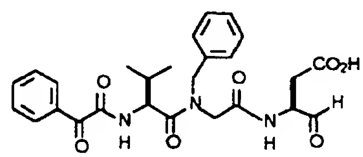
751

3(*S*)-(2-((2(*S*)-(4-Acetylaminobenzoyl)amino-3-methylbutyryl)benzylamino) acetylamino)-4-oxo-butyric Acid (**751**): 3.8 mg (19%) as a white solid: Rt(1) = 8.50 min (98%); (M+H)+ = 525 ($C_{27}H_{32}N_4O_7$ requires 524.6).



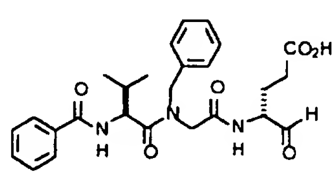
752

3(*S*)-(2(*S*)-(Benzyl(3-methyl-2-(2-oxo-2-(3,4,5-trimethoxyacetylamino)butyryl)amino)acetylamino)-4-oxo-butyric Acid (**752**): 5.0 mg (22%) as a white solid: Rt(1) = 11.09 min (97%); (M+Na)+ = 608 ($C_{29}H_{35}N_3O_{10}$ requires 585.6).



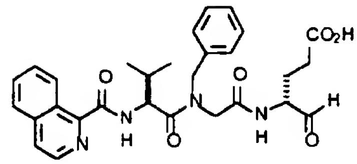
753

3(*S*)-(2(*S*)-(Benzyl(3-methyl-2-(2-oxo-2-phenylacetylamino)butyryl)amino) acetylamino)-4-oxo-butyric Acid (**753**): 3.0 mg (16%) as a white solid: Rt(1) = 11.02 min (96%); (M+Na)+ = 518 ($C_{26}H_{29}N_3O_7$ requires 495.5).



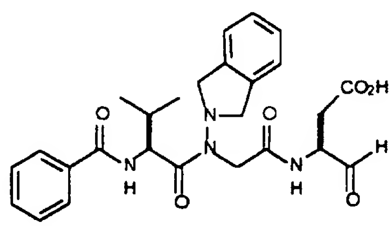
754

4(R)-(2(*S*)-((2-Benzoylamino-3-methylbutyryl)benzyl-amino)acetylamino)-5-oxopentanoic Acid (**754**): 3.5 mg (19%) as a white solid: Rt(1) = 9.56 min (94%); (M+H)+ = 482 ($C_{26}H_{31}N_3O_6$ requires 481.6).



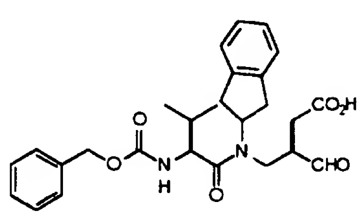
755

4(R)-(2(*S*)-(Benzyl-(2-((isoquinoline-1-carbonyl)amino)-3-methylbutyryl)amino) acetylamino)-5-oxopentanoic Acid (**755**): 6.0 mg (24%) as a white solid: Rt(1) = 10.53 min (93%); (M+H)+ = 533 ($C_{29}H_{32}N_4O_6$ requires 532.6).



756

3(*S*)-(2-((2(*S*)-(Benzoyl)amino-3-methylbutyryl)-(1,3-dihydroisoindol-2-yl)amino)acetylamino)-4-oxo-butyric Acid (**756**): Compound **756** was prepared by a method similar to the method used to prepare compound **724** and compound **706**, except 2-aminoindane was replaced with 2-aminoisoindoline (prepared as described in Eloy, F., Moussebois, C., Bull. Soc. Chim. Belg., 68, pp. 409-421 (1959)).



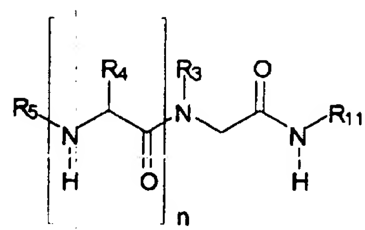
757

3(*S*)-(2-((2(*S*)-(Benzyloxycarbonylamino-3-methylbutyryl)-indan-2-yl)amino)acetylamino)-4-oxobutyric Acid (**757**): was prepared from ((2(*S*)- benzyloxycarbonyl-3-methylbutyryl) indan-2-yl)amino) acetic acid by a method similar to the preparation of **706**: ^1H NMR (CD_3OD) δ 7.4 - 7.5 (m), 7.1 - 7.2 (m), 5.0 - 5.2 (m), 4.8 - 4.95 (dd), 4.5 - 4.7 (m), 3.8 - 4.4 (m), 3.5 (m), 2.9 - 3.4 (m), 2.4 - 2.8 (m), 2.0 - 2.2 (m), 0.90 - 1.15 (m).

CLAIMS

We claim:

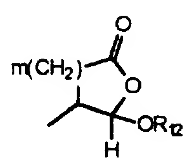
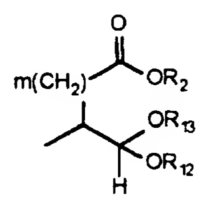
1. A compound represented by the formula:

α 

wherein:

n = 0, 1, or 2;

R_{11} is:

(a)  , or (b)  ;

m is 1 or 2;

R_{12} and R_{13} are independently selected from the group consisting of $-R_7$, $-C(O)-R_7$, and $-C(O)-N(H)-R_7$, or R_{12} and R_{13} taken together form a 4-8-membered saturated cyclic group;

R_2 is -H or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar, -OH, $-OR_7$, -C(O)-OH, $C(O)-NH_2$, or $-OR_5$;

R_7 is selected from the group consisting of -Ar, a $-C_{1-6}$ straight or branched alkyl group optionally

substituted with -Ar, a -C_{1-6} straight or branched alkenyl group optionally substituted with Ar, and a -C_{2-6} straight or branched alkynyl group optionally substituted with Ar;

R_5 is selected from the group consisting of:
-C(O)-R_7,
-C(O)-OR_9,
-C(O)-N(R_9)(R_{10}),
-S(O)$_2$-R_7,
-C(O)C(O)-R_7,
-R_7, and
-H;

each Ar is a cyclic group independently selected from the set consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl and a heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyraxolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, peridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl, and the

aromatic group is optionally singly or multiply substituted with -F, -Cl, -Br, -I, $-OR_{14}$, $-NO_2$, $-S(O_2)-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

each R_{14} is -H or a C_{1-6} straight or branched alkyl group;

each R_9 and R_{10} is independently selected from the group consisting of -H, -Ar, and a C_{1-5} straight or branched alkyl group optionally substituted with -Ar;

each R_4 is a $-C_{1-5}$ straight or branched alkyl group optionally substituted with -Ar or -W;

W is $-OR_9$, $-SR_9$, $-N(H)C(NR_9)N(R_9)(R_{10})$, $-C(O)-OR_9$, or $-N(R_9)(R_{10})$;

R_3 is $-CH_2Ar$ or a 5 to 15-membered non-aromatic cyclic group which contains between 1 and 3 rings, and which optionally contains between 0 and 2 endocyclic oxygen atoms, sulfur atoms, or nitrogen atoms, and wherein the cyclic group is optionally fused with Ar;

provided that when -Ar is substituted with a group containing R_9 or R_{10} which comprises one or more addditional -Ar groups, the -Ar groups are not substituted with a group containing R_9 or R_{10};

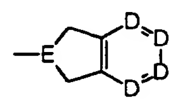
2. A compound according to claim 1, wherein:

R_5 is $-C(O)-R_7$ or $-C(O)C(O)-R_7$;

each R_4 is a C_{1-5} straight or branched alkyl group optionally substituted with Ar;

m is 1;

n is 1;

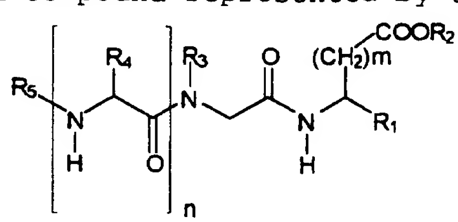
R_3 is $-CH_2Ar$ or 

E is CH or N;

each D is independently N or C, wherein C is optionally substituted with $-OR_{14}$, -F, -Cl, -Br, -I, $-NO_2$, $-S(O)_2-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

each R_9 and R_{10} is independently selected from the group consisting of -H, -Ar, and a $-C_{1-5}$ straight or branched alkyl group optionally substituted with -Ar.

3. A compound represented by the formula:



wherein:

m is 1 or 2;

n is 0, 1, or 2;

R_1 is selected from the group consisting of:
-CN,
-C(O)-H,
-C(O)-CH_2XR_6,
-C(O)-CH_2F,
-C=N-O-R_7, and
-C(O)-R_8;

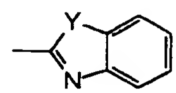
X is selected from the group consisting of O, S, S(O), and $S(O)_2$;

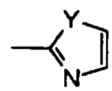
R_6 is independently selected from the group consisting of:
-H,
-$(CH_2)_p$-Ar, and
-C(O)-Ar;

p is 0, 1, 2, or 3;

R_7 is selected from the group consisting of -Ar, a -C_{1-6} straight or branched alkyl group optionally substituted with -Ar, a -C_{1-6} straight or branched alkenyl group optionally substituted with Ar, and a -C_{2-6} straight or branched alkynyl group optionally substituted with Ar;

R_8 is selected from the following group, in which any ring may optionally be singly or multiply substituted by $-NH_2$, -C(O)-OH, -F, -Cl, -Br, -I, -OH, $-NO_2$, -CN, -perfluoroalkyl C_{1-3} alkyl, $-R_5$, $-OR_5$, $-OR_7$, $-N(H)-R_5$, $-N(H)-R_7$, 1,2-methylenedioxy, and $-SR_7$:

(hh)  ; and

(ii)  ;

wherein Y is independently selected from the group consisting of O and S;

each Ar is a cyclic group independently selected from the set consisting of a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl and a heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyraxolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, peridinyl, carbazolyl, acridinyl,

phenazinyl, phenothiazinyl and phenoxazinyl, and the cyclic group is optionally being singly or multiply substituted with $-OR_{14}$, -F, -Cl, -Br, -I, $-NO_2$, $-S(O)_2-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

each R_9 and R_{10} are independently selected from the group consisting of -H, -Ar, and a $-C_{1-5}$ straight or branched alkyl group optionally substituted with Ar;

each R_{14} is -H or a C_{1-6} straight or branched alkyl group;

R_5 is selected from the group consisting of:

$-C(O)-R_7$,
$-C(O)-OR_9$,
$-C(O)-N(R_9)(R_{10})$,
$-S(O)_2-R_7$,
$-C(O)C(O)-R_7$,
$-R_7$, and
-H;

R_4 is a $-C_{1-5}$ straight or branched alkyl group optionally substituted with Ar or W;

W is $-OR_9$, $-SR_9$, $-N(H)C(NR_9)N(R_9)(R_{10})$, $-C(O)-OR_9$, and $-NR_9,(R_{10})$;

R_3 is $-CH_2Ar$ or a 5 to 15-membered non-aromatic cyclic group which contains between 1 and 3 rings, and which optionally contains between 0 and 2 endocyclic

oxygen atoms, sulfur atoms, or nitrogen atoms, and wherein the cyclic group is optionally fused with Ar;

R_2 is -H, or a C_{1-6} straight or branched alkyl group, wherein the alkyl group is optionally substituted with Ar, -OH, $-OR_7$, -C(O)-OH, $C(O)-NH_2$, or $-OR_5$;

provided that when -Ar is substituted with a group containing R_9 or R_{10} which comprises one or more addditional -Ar groups, the -Ar groups are not substituted with a group containing R_9 or R_{10};

4. A compound according to claim 3, wherein:

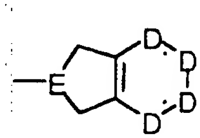
R_1 is -C(O)-H;

R_5 is $-C(O)-R_7$ or $-C(O)C(O)-R_7$;

R_4 is a $-C_{1-5}$ straight or branched alkyl group optionally substituted by -Ar;

m is 1;

n is 1;

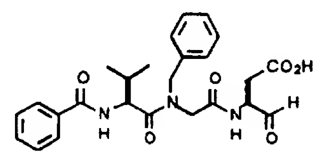
R_3 is $-CH_2Ar$, or 

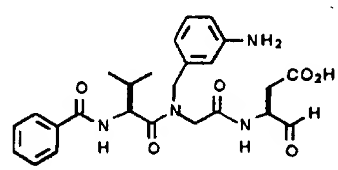
E is CH or N;

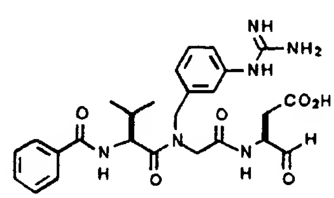
each D is independently N or C, wherein C is optionally substituted with $-OR_{14}$, -F, -Cl, -Br, -I, $-NO_2$, $-S(O)_2-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

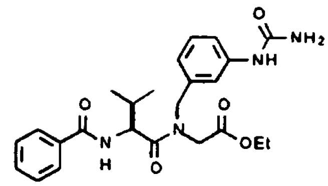
each R_9 and R_{10} is independently selected from the group consisting of -H, -Ar, and a $-C_{1-5}$ straight or branched alkyl group optionally substituted with -Ar.

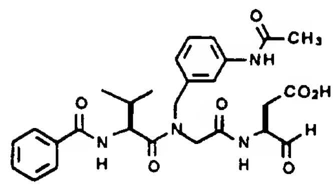
5. The compound according to claim 4 selected from the group consisting of:

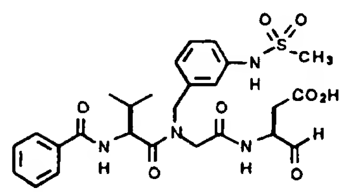
706  ;

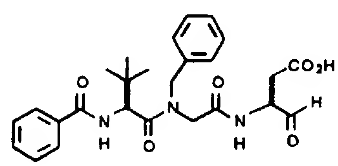
737  ;

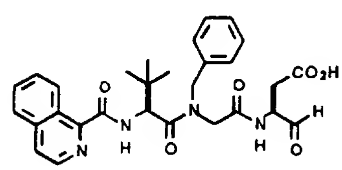
739  ;

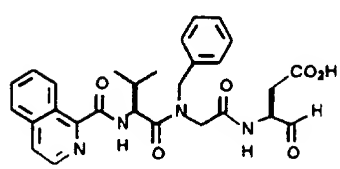
741  ;

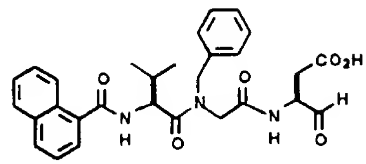
743  ;

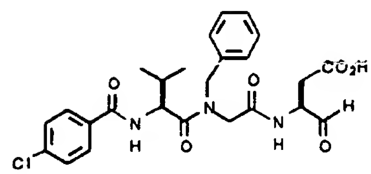
745  ;

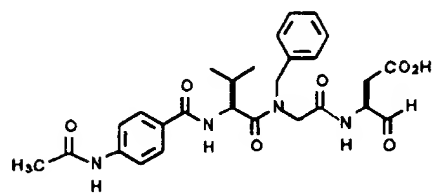
746  ;

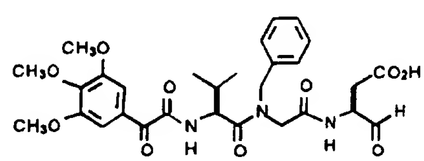
747  ;

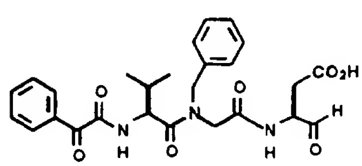
748  ;

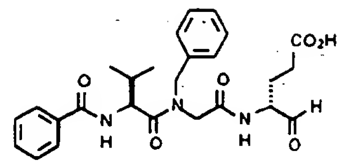
749  ;

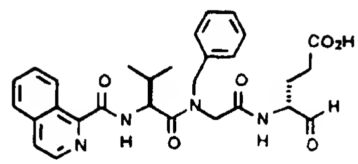
750  ;

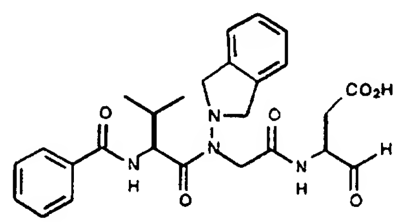
751  ;

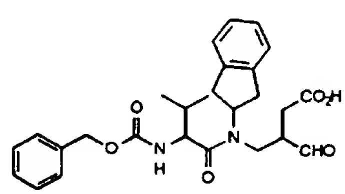
752  ;

753  ;

754  ;

755  ;

756  ; and

757  .

6. A compound according to claim 3, wherein:

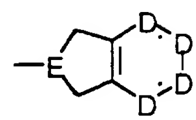
R_1 is $-C(O)-R_8$;

R_5 is $-C(O)-R_7$ or $-C(O)C(O)-R_7$;

R_4 is a $-C_{1-5}$ straight or branched alkyl group optionally substituted by -Ar;

m is 1;

n is 1;

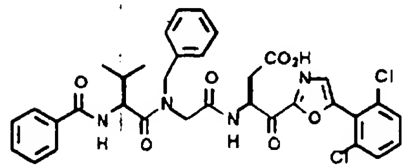
R_3 is $-CH_2Ar$, or 

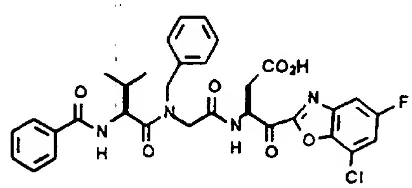
E is CH or N;

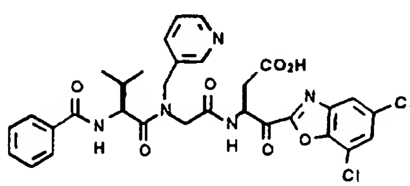
each D is independently N or C, wherein C is optionally substituted with $-OR_{14}$, -F, -Cl, -Br, -I, $-NO_2$, $-S(O)_2-N(R_9)(R_{10})$, $-C(O)-N(R_9)(R_{10})$, $-N(H)-C(O)-N(R_9)(R_{10})$, $-N(R_9)(R_{10})$, $-C(O)-OR_9$, $-CF_3$, $-OCF_3$, a C_{1-6} straight or branched alkyl group, 1,2-methylenedioxy, -CN, or $-N(H)C(NR_9)N(R_9)(R_{10})$;

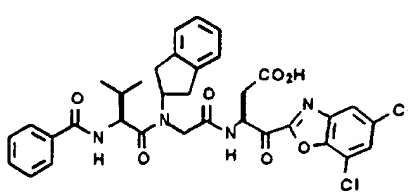
each R_9 and R_{10} is independently selected from the group consisting of -H, -Ar, and a $-C_{1-5}$ straight or branched alkyl group optionally substituted with -Ar.

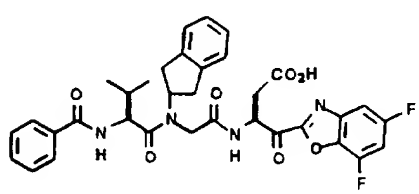
7. The compound according to claim 6 selected from the group consisting of:

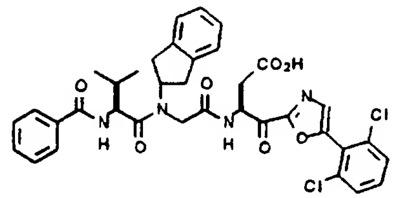
710  ;

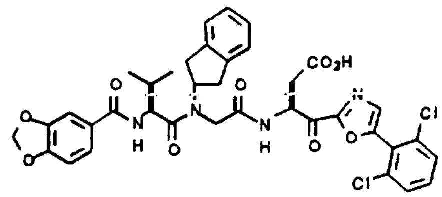
719  ;

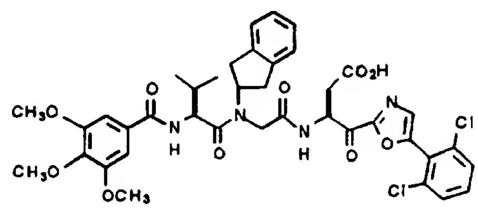
720  ;

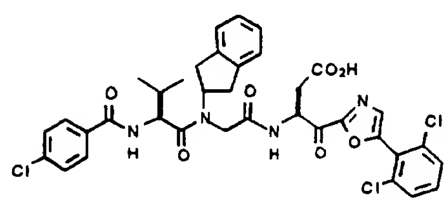
725  ;

726  ;

727  ;

729  ;

731  ; and

733  .

8. A compound according to claim 3, wherein R_1 is $-C(O)-CH_2XR_6$.

9. A pharmaceutical composition comprising an ICE inhibitor according to any one of claims 1-8 in an amount effective for treating or preventing an IL-1-

mediated disease and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition comprising an ICE inhibitor according to any one of claims 1-8 in an amount effective for treating or preventing an apoptosis-mediated disease and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition according to claim 9, wherein the IL-1-mediated disease is an inflammatory disease selected from the group consisting of osteoarthritis, pancreatitis, asthma, and adult respiratory distress syndrome.

12. The pharmaceutical composition according to claim 11, wherein the inflammatory disease is osteoarthritis or acute pancreatitis.

13. The pharmaceutical composition according to claim 9, wherein the IL-1-mediated disease is an autoimmune disease selected from the group consisting of glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, and graft vs host disease.

14. The pharmaceutical composition according to claim 13, wherein the autoimmune disease is

rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or psoriasis.

15. The pharmaceutical composition according to claim 9, wherein the IL-1-mediated disease is a bone destructive disorder, wherein the disorder is osteoporosis or a multiple myeloma-related bone disorder.

16. The pharmaceutical composition according to claim 9, wherein the IL-1-mediated disease is a proliferative disorder selected from the group consisting of acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

17. The pharmaceutical composition according to claim 9, wherein the IL-1-mediated disease is an infectious disease, selected from the group consisting of sepsis, septic shock, and Shigellosis.

18. The pharmaceutical composition according to claim 9, wherein the IL-1-mediated disease is a degenerative or necrotic disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia.

19. The pharmaceutical composition according to claim 18, wherein the degenerative disease is Alzheimer's disease.

20. The pharmaceutical composition according to claim 10, wherein the apoptosis-mediated disease is

a degenerative disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

21. A pharmaceutical composition for inhibiting an ICE-mediated function comprising an ICE inhibitor according to any one of claims 1-8 and a pharmaceutically acceptable carrier.

22. A method for treating or preventing a disease selected from the group consisting of an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a proliferative disorder, an infectious disease, a degenerative disease, a necrotic disease, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular

atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke in a patient comprising the step of administering to said patient a pharmaceutical composition according to any one of claims 9 to 21.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/20370

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/00 A61K38/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 23, 11 November 1994, WASHINGTON US, pages 3863-6, XP000652064 DOLLE, ROLAND E. ET AL: "Aspartyl.alpha.-((1-Phenyl-3-(trifluoromethyl)- pyrazol-5-yl)oxy)methyl Ketones as Interleukin-1.beta. Converting Enzyme Inhibitors. Significance of the P1 and P3 Amido Nitrogens for Enzyme-Peptide Inhibitor Binding" see the whole document ---	1-22
X	EP 0 644 198 A (STERLING WINTHROP INC) 22 March 1995 see the whole document ---	1-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
14 April 1997	14.05.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chakravarty, A

INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/US 96/20370

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOORG. MED. CHEM. LETT. , vol. 4, no. 19, 1994, pages 2359-2364, XP000653042 MULLICAN, MICHAEL D. ET AL: "The synthesis and evaluation of peptidyl aspartyl aldehydes as inhibitors of ICE" see the whole document ---	1-22
P,X	WO 95 35308 A (VERTEX PHARMA) 28 December 1995 see the whole document ---	1-22
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 5, 1994, WASHINGTON US, pages 563-564, XP002029379 DOLLE R.E. ET AL.: "P1 Aspartate-based peptide alpha-(2,6-dichlorobenzoyl)oxy)methyl ketones as potent time-dependent inhibitors of interleukin 1-beta-converting enzyme" see the whole document -----	1-22

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/20370

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 1-4,6,8,9-22.
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See attached sheet

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Claims 1-4, 6 and 8 of the present patent application do not comply with the requirements of Article 6 PCT to such an extent that it is not possible to carry out a complete search.

The Guidelines say explicitly that "no special search effort need be made for searching unduly wide or speculative claims" [Guidelines B-III, 3.7 and 3.12]., and that the costs for the search are to be "kept within reasonable bounds" [Guidelines B-IV, 2.8].

Claims 1-4, 6 and 8 fail to adequately indicate the structure of the subject-matter for which protection is sought. The long list of variables with cascading significances, ill-defined substituents and disclaimers, cannot be regarded as a "clear and concise description of the matter for which protection is sought".

The search has therefore been limited to the subject-matter of claims 5, 7 and corresponding subject-matter of claims 9-22 [see Art. 17(2)(a)ii PCT] as well the compounds explicitly mentioned in the Examples.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/20370

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0644198 A	22-03-95	AU 6347394 A	27-04-95
		CZ 9401355 A	15-12-94
		FI 942624 A	04-12-94
		HU 68689 A	28-07-95
		JP 7089951 A	04-04-95
		NO 942064 A	05-12-94
		NZ 260669 A	21-12-95
		SK 67394 A	11-07-95
		US 5585357 A	17-12-96
WO 9535308 A	28-12-95	AU 2944695 A	15-01-96
		CA 2192089 A	28-12-95
		FI 965036 A	14-02-97